Range, quality, and costs of antimalarial drugs available in the retail sector in Kenya

Thesis

Range, quality, and costs of antimalarial drugs available in the retail sector in Kenya.

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ABSTRACT

Background: The main strategy for rolling back malaria in Africa is prompt, presumptive treatment of fever among those at risk. Most fevers in Africa are treated first with antipyretic or antimalarial drugs obtained from the retail sector. The objectives of the thesis were to understand retail provision of antimalarial drugs, drug use patterns and quality in four communities in Kenya to enable an exploration of impediments to effective antimalarial drug use in Kenya and how these might be redressed in the national antimalarial drug policy.

Methods: The thesis used an eclectic mix of methods: from review of policy documents; key informant interviews; laboratory-based pharmaceutical analytical techniques; mathematical modeling of effectiveness; to structured questionnaires administered to households/retailers in four districts of Kenya.

Results: The community survey revealed that less than 3% of children below five years accessed sulfadoxine/pyrimethamine (SP), the first-line drug. Adult and paediatric doses of SP and amodiaquine (AQ, second-line) in the retail retail sector were less than one US dollar; that of the new first-line drug, artemether-lumefantrine (ART-LUM) was eight US dollars. Less than a third of the retailers knew the correct dose of AQ for an adult and even less (2%) could state the correct dose for a child of 2 years. About 41% of SP and AQ products sampled from the retail sector were sub-standard. The modeled effectiveness of SP and AQ was found to be 51 and 45%, respectively, when drug quality, use, and adherence were taken into consideration; that of ART-LUM was approximately 85%.

Conclusions: Effective drugs are not a panacea to therapy of malaria if they remain inaccessible to rural populations at risk in Kenya. The RBM targets on prompt, effective

treatment of fevers are unlikely to be met without an increased investment in behaviour change initiatives and provision of effective and affordable therapeutics at all levels of the health service, including the retail sector.

DEDICATION

To my parents,

Fatuma Hassan Nur

and

Abass Amin Ali

"...I did then, what I knew how,

I will do better, when I know better"

(Maya Angelou)

TABLE OF CONTENTS

LIST OF TABLES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

LIST OF FIGURES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

LIST OF APPENDICES

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ABBREVIATIONS

ACPR ..... Adequate Clinical and Parasitological Response
ACR ..... Adequate Clinical Response
ACTs ..... Artemisinin-based Combination Therapies
AC ..... Anti-cough
AD ..... Anti-diarrhoeal
AFRO ..... World Health Organization Africa Regional Office
AH ..... Anti-helminthic
AM ..... Antimalarial
AMREF ..... African Medical Research Foundation
AP ..... Antipyretic
API ..... Active Pharmaceutical Ingredient
AQ ..... Amodiaquine
ARMA ..... Atlas du Risqué de Malarie en Afrique
ART ..... Artemisinin derivatives
ART-LUM ..... Artemether-Lumefantrine
AS ..... Artesunate
BOMA ..... Burden of Malaria in Africa
BP ..... British Pharmacopoeia
CBK ..... Central Bank of Kenya
CBS ..... Central Bureau of Statistics
CDA ..... Chlorproguanil-Dapsone-Artesunate
CDC ..... Centers for Disease Control
CDR ..... Committee for Drug Registration
CHW ..... Community Health Workers
CP ..... Chief Pharmacist
CPP ..... Certificate of Pharmaceutical Product
CQ ..... Chloroquine
CRS ..... Catholic Relief Services
DARU ..... Drug Analysis and Research Unit
DDT ..... Dichloro-Diphenyl-Trichloroethane
DfID ..... Department for International Development
DH ..... District Hospital
DHFR ..... Dihydrofolate reductase
DHMBs ..... District Health Management Boards
DHMT ..... District Health Management Team
DHPS ..... Dihydropteroate synthase
DMOH ..... District Medical Officer of Health
DMS ..... Director of Medical Services
DOMC ..... Division of Malaria Control
DPTWG ..... Drug Policy Technical Working Group
DRA ..... Drug Regulatory Authority
DVBD ..... Division of Vector Borne Diseases
EA ..... Enumeration Area
EANMAT ..... East African Network for Monitoring Antimalarial Treatment
EPV ..... Events Per Variable
ETF ..... Early Treatment Failure
FW ..... Field Worker
GCP ..... Good Clinical Practice
GDP ..... Gross Domestic Product
GFATM ..... Global Fund for AIDS, Tuberculosis, and Malaria

GIS ..... Geographic Information Systems
GMP ..... Good Manufacturing Practices
GoK ..... Government of Kenya
GPS ..... Global Positioning System
GTZ ..... German Technical Cooperation Agency
HAL ..... Halofantrine
HMIS ..... Health Management Information Systems
HPLC ..... High Pressure Liquid Chromatography
IEC ..... Information, Education, and Communication
IMCI ..... Integrated Management of Childhood Illness
INN ..... International Non-proprietary Name
IPT ..... Intermittent Presumptive Treatment
IQR ..... Inter-quartile Range
ITN ..... Insecticide Treated Bed nets
JSI ..... John Snow Inc
KEDL ..... Kenya Essential Drugs List
KEMRI ..... Kenya Medical Research Institute
KEMSA ..... Kenya Medical Supplies Agency
KENAAM ..... Kenya NGO's Alliance Against Malaria
KEPI ..... Kenya Enhanced Programme for Immunisation
KES ..... Kenya Shilling
KNDP ..... Kenya National Drug Policy
KNDPIP ..... Kenya National Drug Policy Implementation Programme
KNH ..... Kenyatta National Hospital
KNMS ..... Kenya National Malaria Strategy
LC ..... Label Claim
LMICs ..... Low- and Middle-Income Countries
LPF ..... Late Parasitological Failure
LQAS ..... Lot Quality Assurance Sampling
LTF ..... Late Treatment Failure
MARA ..... Mapping malaria Risk in Africa
MCU ..... Malaria Control Unit
MEDS ..... Mission for Essential Drugs and Supplies
MEF ..... Mefloquine
MoF ..... Ministry of Finance
MoH ..... Ministry of Health
MSCU ..... Medical Supplies Coordinating Unit
MSF ..... Medicins Sans Frontieres
NAO ..... National Audit Office
NCPD ..... National Council for Population and Development
NGOs ..... Non-governmental organizations
NHIF ..... National Health Insurance Fund
NLTP ..... National Leprosy and TB Programme
NMCP ..... National Malaria Control Programme
NQCL ..... National Quality Control Laboratory
OPD ..... Out-patient Diagnosis
OTC ..... Over-the-counter
OTH ..... Other
PCA ..... Population Communication Africa
PGH ..... Provincial General Hospital
PHPs ..... Public Health Products
PMT ..... Pyrimethamine
POM ..... Prescription-only-Medicine

PPB.....Pharmacy and Poisons Board
PQ.....Primaquine
PRO.....Proguanil
PS .....Permanent Secretary
PSI.....Population Services International
PSK .....Pharmaceutical Society of Kenya
QC .....Quality Control
QN.....Quinine
RBM.....Roll Back Malaria
SDH.....Sub-district Hospitals
SDX.....Sulfadoxine
SMS.....Scientific Media Services
SP .....Sulfur-pyrimethamine or sulfadoxine-pyrimethamine
TET .....Therapeutic Efficacy Testing
TOT.....Training of Trainers
UK.....United Kingdom
UNDP.....United Nations Development Programme
UNICEF .....United Nation Children's Fund
USD.....United States Dollar
USP .....United States Pharmacopoeia
UTL.....Useful Therapeutic Life
UV.....Ultra Violet Spectroscopy
WHO .....The World Health Organization

CHAPTER 1:

Introduction and literature review

1.1 Introduction

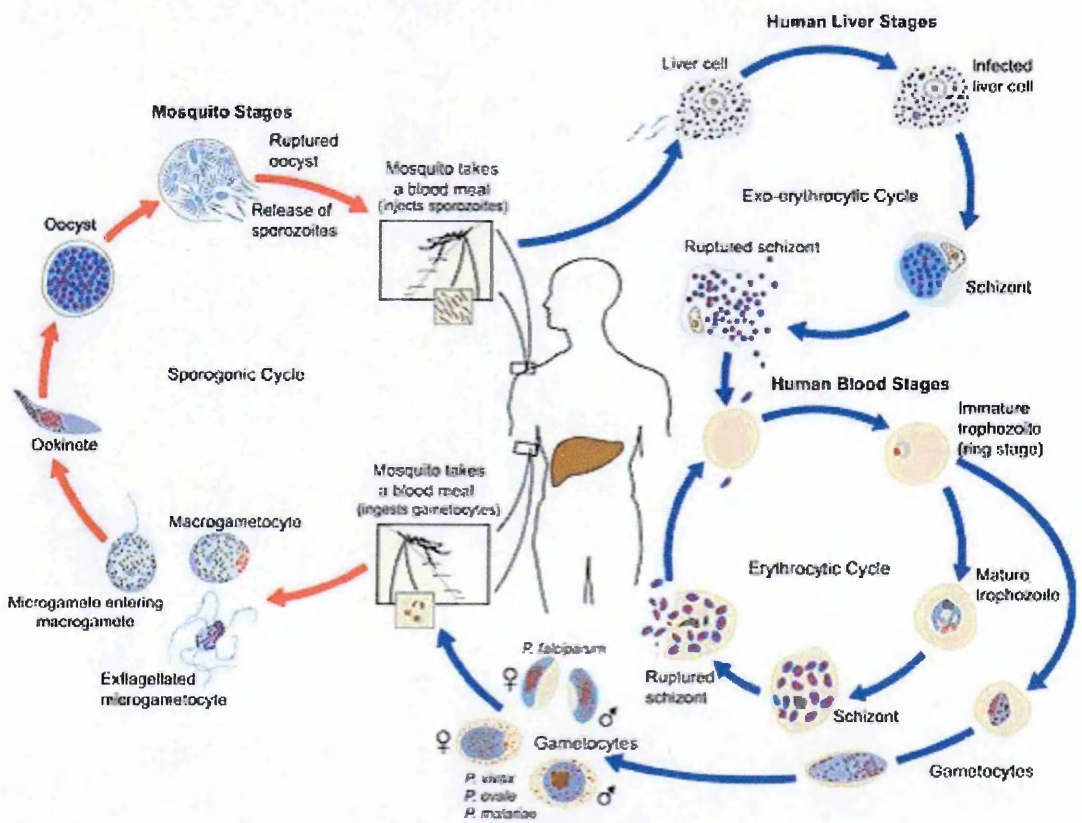
This chapter presents a broad overview of a number of issues around effective use of antimalarial drugs. A context for the issues is provided by reviewing the literature on the burden of malaria especially in sub-Saharan Africa and the consequences of *P. falciparum* infection (the principal malaria parasite in Africa and the most virulent), the historical context of malaria control and contemporary approaches to malaria control. Especially important is the Roll Back Malaria initiative and case management of clinical cases of malaria as the cornerstone of rolling back malaria globally. The challenges posed to appropriate case management by drug resistance are reviewed. Lastly, determinants of effective drug use (quality, efficacy, and appropriate use) are reviewed with a view to identifying research gaps that are pertinent to Kenya (the location for the thesis), which are contextually explored in more detail in Chapter 2.

1.2 Malaria: parasite life cycle, clinical presentation, and practical considerations

Human malaria is caused by four genetically recognised species of the genus *Plasmodium –P. falciparum, P. ovale, P. malariae, and P. vivax-* and transmitted by infected females of the *Anopheles* mosquito. Except *P. malariae*, which might infect higher primates, the other three are exclusively parasites of man. There are two broad phases of the *Plasmodium* life cycle, a sexual replication (sporogony) within the mosquito and an asexual one (schizogony) within the human (Gilles, 1993). In the first phase, the mosquito ingests male and female gametocytes (micro- and macro-gametocytes, respectively) while taking a blood meal from an infected human. These undergo maturation within the mosquito, then come together during fertilization in the gut of the mosquito to form a globular zygote. The zygote, which is initially immotile, becomes elongated and motile to form an oökinete. The oökinete then invades the midgut wall of the mosquito to develop into a static oöcyst. After

maturation, the oöcyst ruptures to release motile sporozoites which migrate to the mosquito salivary glands and are injected into humans during the next blood meal (Garnham, 1988). In the human, sporozoites, which survive the body's defences, invade the liver cells and enter into the exo-erythrocytic stage, which culminates in the rupture of the resultant schizont releasing thousands of merozoites into the blood stream. In *P. vivax* and *P. ovale,* some sporozoites remain in liver cells to form hypnozoites, which often lead to relapsing malaria. Circulating merozoites infect red blood cells (erythrocytic stage). Merozoites develop within the erythrocytes from where they are released periodically into the blood stream to infect more and more red cells. Some merozoites differentiate into gametocytes, which are ingested by mosquitoes during a blood meal; ingested gametocytes go through a cycle of maturation within the mosquito gut to form sporozoites, which infect hosts in the next blood meal (Figure 1.1).

Figure 1.1: Life cycle of *Plasmodium* in man and in the mosquito (http://www.cdc.gov/malaria/biology/life_cycle.htm, accessed 20/12/04).



Malaria is an acute febrile illness with diverse clinical presentations. Many of its signs and symptoms (e.g. fever, headache, nausea) are non-specific and are common to other infectious febrile diseases, such as typhoid fever and upper respiratory tract infection and invariably, algorithms to interpret malaria illness are not generalisable and therefore pose problems for unique malaria diagnosis (Rooth & Bjorkman, 1992; Redd *et al.*, 1996; Weber *et al.*, 1997; Olaleye *et al.*, 1998; Muhe *et al.*, 1999; Bojang *et al.*, 2000; Chandramohan *et al.*, 2002). Difficulties in diagnosis are compounded by the fact that most people living in endemic areas carry malaria parasites in their blood without developing overt symptoms of clinical malaria, i.e. not all those with circulating parasites in their blood have malaria, and not all fevers are malaria.

Despite difficulties in diagnosis, however, malaria typically presents as a febrile paroxysm characterised by a progression from feeling cold, then hot, and finally heat loss by way of profuse sweating. Paroxysms are coincident with the rupture of mature erythrocytic schizonts and are punctuated by periods of wellness, which are varied depending on the species of *Plasmodium.* For *P. falciparum*, paroxysms occur every other day (Wernsdorfer & McGregor, 1988). The majority of people living in malaria endemic countries (much of Africa) develop uncomplicated malaria and recover spontaneously or with the help of antimalarial drugs. However, a small proportion, particularly of non-immune children will progress to severe disease (Snow & Marsh, 2002), characterised mostly by three syndromes: impaired consciousness, severe respiratory distress and severe anaemia (Marsh *et al.*, 1995), and some may eventually die.

Although fever is a non-specific symptom of malaria, and there are those who question its utility (Einterz & Bates, 1997), it is an important diagnostic and management tool in Africa because it is the single most important prompt for seeking treatment among populations in the continent. The World Health Organization (WHO) advocates presumptive diagnosis of

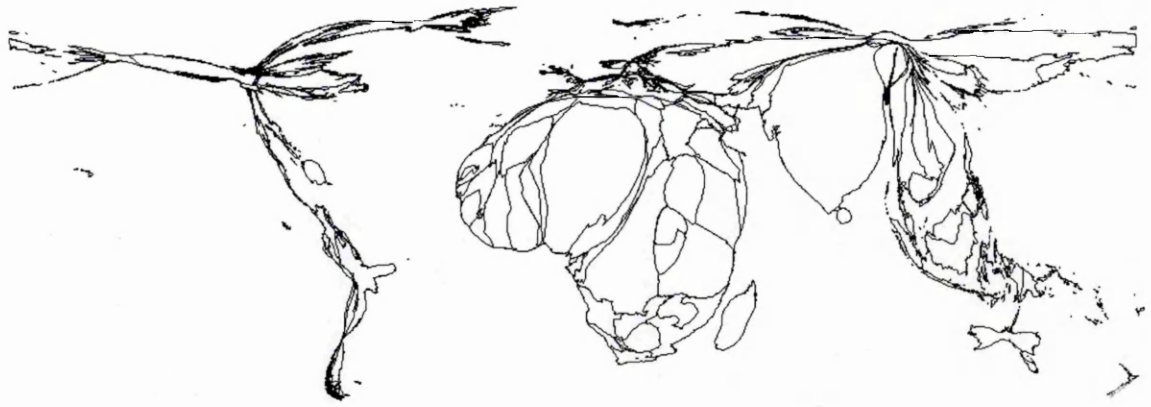
fever as "malaria" among children under five years living in malaria endemic areas (WHO, 1986). This policy has been criticised by some as wasteful, since more children are treated than those who require antimalarial drugs (Olivar *et al.*, 1991; Massaga *et al.*, 1999), but remains practicable in Africa where laboratory and clinical facilities are wanting.

Snow *et al.* (2003) contend that the incidence of perceived fever is more important than the precise incidence of clinical malaria when examining the demand for services. They estimate that the age-structured annual burden of fever in 41 sub-Saharan African countries among children below 5 years of age is 0.85 billion cases, 0.64 billion cases among the 5 to 14 year age group, and 1.35 cases among adults. They also show that, although the burden of malaria is borne mostly by children below the age of five, adults and older children still seek treatment for fever, treated as malaria, despite a low biological risk.

1.3 Global malaria burden

Malaria remains a major cause of death and disability worldwide and is endemic to much of Africa, South America, and Southeast Asia. Other malaria risk areas include the Middle East, some countries in Central America and Polynesia, with most other continents virtually free of the disease (Figure 1.2). In a 5-year Global Burden of Disease Study, Murray & Lopez (1997a) estimated that infectious and parasitic diseases (malaria included) explained 22.9% of global disability-adjusted life years (DALYs). More specifically, malaria was ranked as the 11th most common cause of death globally and accounted for 856,000 deaths in 1990 alone (Murray & Lopez, 1997b). Even such high estimates and the higher and hackneyed "one-million deaths due to malaria annually" (Bruce-Chwatt, 1952) are thought to be conservative; recent empirical data suggest that the true burden of malaria is much higher especially in Africa, and rising, rather than declining (Snow *et al.*, 1999; 2001a; 2003).

Figure 1.2: The national falciparum prevalence (N*f*P*) cartogram for 2002 (Hay *et al.*, 2004).



* Using data from a variety of sources a national prevalence (NP) was estimated by: (population exposed to hypoendemic x 0·05) + (population exposed to mesoendemic x 0·305) + (population exposed to hyperendemic x 0·63) + (population exposed to holoendemic x 0·875). The product of the NP and the 1993 *P. falciparum* index then gives a national falciparum prevalence (N*f*P). Figure is weighted by population exposed to risks.

1.4 Burden of Malaria in Africa (BOMA)

The greatest burden of malaria lies in Africa south of the Sahara. Of an estimated 90-500 million global cases of malaria reported annually, 90% occur in Africa (WHO, 1992). However, this view is increasingly being challenged with recent research showing that indeed the burden of malaria is higher than previously thought in Southeast Asia, where this region accounts for 25% of global clinical attacks due to *P. falciparum* (Snow *et al.*, 2005). Majority of malaria cases in Africa are due to *P. falciparum* (Brinkmann & Brinkmann, 1991) and occur mostly in children (Snow *et al.*, 1999).

1.4.1 Morbidity and mortality due to malaria

Malaria has both direct and indirect consequences. Through a combination of empirical survey-derived data and modelling, Snow *et al.*, (1999) have estimated that 987,466 people (including 765,442 children) may have died of the direct consequences of *P. falciparum* infection in sub-Saharan Africa in 1995. They also estimate that 207.5 million clinical attacks of malaria may have occurred among people living under stable endemic conditions in Africa in the same year.

Chronic sub-clinical malaria infections predispose to anaemia or under-nutrition, which in turn lead to an increased susceptibility to general infections. Guyatt & Snow (2001a) have estimated that as many as 400,000 pregnant women in sub-Saharan Africa may have developed anaemia as a result of malaria infection in 1995, predisposing to low birth weight and premature mortality among children born to such women (Guyatt & Snow, 2001b). Anaemic mothers face the risk of HIV infections since they might require blood transfusion.

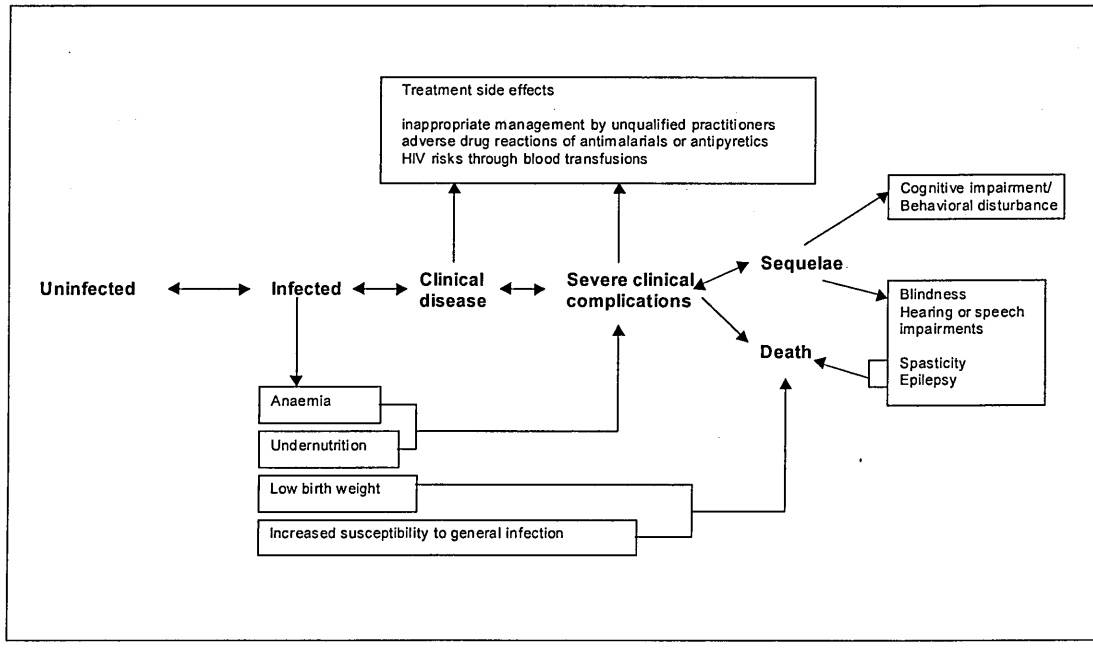
It is common practice for most communities in Africa to self-medicate for fevers and malaria, using sub-optimal doses of antimalarial or antipyretic drugs (Section 1.8). Even when they are seen by formal, qualified health workers, such people can be prescribed drugs inappropriately (Zurovac *et al.*, 2004). A combination of poor health seeking behaviour and inappropriate use of drugs increases patients' chances of experiencing adverse drug reactions, which exacerbate the malaria illness. Those who experience severe complications of the malaria illness and survive may experience overt effects like blindness or epilepsy or more subtle neurological sequealae such as behavioural and cognitive impairment (Holding *et al.*, 1999; Holding & Snow, 2001). These overt and hidden burdens of malaria in Africa are summarised in Figure 1.3.

1.4.2 Economic burden of malaria

In the past few decades, development partners (as part of structural adjustment programmes) in Africa have called for public sector reforms. Consequently, African governments have had to cut back on health expenditure to equitably finance other sectors of the economy. This means that households in Africa have had to pay more and more to access healthcare and malaria is no exception. Not only is direct household expenditure on malaria high (Ettling *et al.*, 1994; Asenso-Okyere & Dzator, 1997; Asenso-Okyere *et al.*, 1998; Chima *et al.*, 2003), but malaria has also had a deleterious effect on economic

prosperity on the continent in general. Gallup & Sachs (2001) have shown that in 1995 alone, countries with "intensive malaria" had on average, income levels 33% that of countries without malaria when controlled for other confounding factors, and that countries where malaria was eliminated had since shown a substantial increase in economic growth compared to neighbouring malarious countries. They argue therefore that malaria is a major cause of poverty in Africa.

Figure 1.3: Direct and indirect consequences of *P. falciparum* malaria infection (Snow & Gilles, 2002)



1.5 Malaria control initiatives

1.5.1 History of malaria control

Following the elucidation of the link between malaria, *Plasmodia* and *Anopheles* mosquitoes through the discoveries of Ronald Ross and various researchers (largely Italian malariologists) and the discovery of highly efficacious synthetic and natural insecticides (organochlorines like DDT and the permethrins for instance), efforts to eradicate the vector from human habitations were made. Most notable were the large-scale global malaria eradication programmes undertaken by the WHO in the 1950s and 1960s. These were

carried out in parts of North America, Europe and Asia with mixed success; malaria was successfully eradicated from much of the temperate world (Europe, North America and Australia) and some Asian countries (Dobson, 1999).

In Africa, such programmes were contentious from the beginning since some researchers argued that they would lead to loss of natural immunity and subsequent resurgence of malaria should the control strategies fail to be sustained. Further, it has been argued that programmes at best were patchy and uncoordinated and failed because of lack of commitment (Dobson *et al.*, 2000). In Kenya, as in the rest of Africa, vector eradication programmes were tried (notably in Kisumu and Taveta) without much success (Garnham, 1929; Smith & Draper, 1959; Fontaine *et al.*, 1978). It was generally accepted that malaria eradication was unsustainable in areas of high transmission (most of Africa) and that a more suitable method would be malaria control using efficacious tools such as personal protection and chemotherapy.

Antimalarial drugs also played an important role in the control of malaria. Historically, they have been used in three ways: in the treatment of clinical cases of malaria, in the prevention of malaria or chemoprophylaxis and in aid of the vector eradication schemes of the 1950s and 1960s. In the latter, antimalarial drugs were used in three ways: in the presumptive treatment of suspected malaria cases, the radical treatment of confirmed cases and mass drug administration, either directly by distribution of drugs or indirectly in the form of medicated salt (Beales, 1988). The use of antimalarial drugs in malaria eradication has fallen by the wayside, but more recently intermittent presumptive treatment, especially among pregnant women has received renewed interest (van Eijk *et al.*, 2004). In Kenya for instance, this has been incorporated into the Kenya National Malaria Strategy to help reduce morbidity and mortality due to malaria.

1.5.2 Contemporary control strategies

Following the eradication of malaria from much of the temperate (and developed) world, malaria is now largely a disease of the tropics. Two contemporary approaches are being promoted in the control of malaria in Africa: use of insecticide treated bed nets (ITN) in the prevention of malaria and appropriate case management of malaria using safe, efficacious antimalarial drugs.

1.5.2.1 Roll Back Malaria (RBM)

The arguments concerning failure of the global malaria eradication programmes notwithstanding, emphasis on malaria control in the last few decades has slowly shifted to effective management of disease outcomes. Interest in malaria control has re-emerged through the impetus provided by the Roll Back Malaria (RBM) movement, a global partnership jointly founded by WHO, UNICEF, The World Bank and UNDP and launched in November 1998 by WHO in conjunction with African Heads of State in Abuja, Nigeria. The RBM initiative's key objective is to halve malaria morbidity and mortality by the year 2010 (Nabarro & Taylor, 1998). To attain this objective, four core strategies have been promulgated: 1) rapid, effective treatment of persons with malaria as close to home as possible within the first 24 hours; 2) increased use of ITN to limit human-mosquito contact; 3) prevention of malaria in pregnancy and 4) better epidemic preparedness and appropriate response (www.rbm.who.int, accessed 20/12/04). Following the launch of RBM, several African governments have adopted these core strategies as part of their malaria control activities. In Kenya, RBM strategies form the basis of the Kenya National Malaria Strategy discussed in Section 2.4.2.

1.5.2.2 Insecticide treated bed nets (ITN)

ITN represent an old method which has been given a new lease of life in the past 15 years (Dobson *et al.*, 2000). Several studies have demonstrated the efficacy of ITN in a variety of

African settings. In a recent Cochrane review of the efficacy of ITN, Lengeler (2004) demonstrates that ITN provided protective efficacy against child mortality of 17% compared to no nets, and 23% compared to untreated nets and reduced the incidence of uncomplicated malaria, severe malaria, parasite prevalence, high parasitaemia, splenomegaly, and anaemia. ITN have therefore been adopted as a key strategy in malaria control in many malaria endemic countries, alongside effective case management of febrile events.

1.5.2.3 Case management

Despite the significance of reducing the risks of infection through ITN, many believe that the foundation to any successful efforts to reduce the mortality burden posed by malaria will be through effective case-management of febrile illness (Marsh, 1998; Trape *et al.* 2002; Snow & Marsh 2002). Case management has prompt diagnosis and effective management as its key pillars. These pillars in turn rest on the adherence to good clinical practices usually espoused in national and international treatment guidelines that use best evidence to define standards of care. Good clinical practice in turn requires a well-functioning health care system, which readily and equitably avails effective drugs and medical supplies and sufficient numbers of well-trained health care personnel to deliver services to populations in need.

Under the RBM core strategies case management involves rapid, effective treatment of cases as close to home as possible. A number of guidelines have been developed in this respect, both at national and international levels. Nationally, standard treatment guidelines have been promoted as part of the broader essential drugs concept. In Kenya for instance, a national guideline for the diagnosis and management of malaria has been developed and has been in use since 1998 (DOMC, 1998). Internationally, such guidelines are increasingly being harmonised with efforts to manage sick children under the Integrated

Management for Childhood Illness (IMCI) developed by WHO and UNICEF (WHO, 2000a).

Whilst an apparently simple strategy, the majority of the African continent has a number of distinguishing features which make case-management of malaria complex. Malaria is a common illness, most frequently occurring as a minor illness, especially among immune adult populations. It may not therefore be perceived as a high-risk disease. Diagnosis of malaria is difficult; resources to make a parasitological diagnosis, and algorithms to interpret the findings, present management problems, especially in endemic settings (Section 1.2). At the same time, rapid clinical deterioration and death are a common feature of malaria cases, implying a narrow window of opportunity for instituting effective treatment in these most severe cases (Greenwood *et al.,* 1987). The greatest burden of disease occurs in resource-poor environments, where geographic access to government health facilities is limited, and both regulatory and communication strategies are compromised. This commonly leads to inappropriate treatment strategies being adopted, for those seeking treatment through the formal health sector and the retail sector (Section 1.8). Inadequate resources further compromise regulatory strategies, and lead to widely varying quality amongst available antimalarial drugs, especially within the private retail sector (Chapters 3 and 6). Additional complications derive from emerging antimalarial drug resistance, and the lack of cheap, safe, and efficacious replacements (Chapter 2).

1.6 Drugs used to treat malaria

A wide range of drugs is available in the chemotherapy of malaria (Table 1.1). In the literature, antimalarial drugs are largely classified using either their chemical properties (chemical classification) or their biological properties (bio-functional classification), although mode of action (antifolates) is sometimes cited. In the bio-functional

classification, drugs that kill schizonts of the malaria parasite for instance are termed schizontocides, those that kill the gametocytes are termed gametocytocides, and so on (Reynolds, 1993; Warrell *et al.*, 2002).

Table 1.1: Summary of selected characteristics of contemporary registered antimalarial drugs (WHO, 2000b)

Option	**Effective against *P. vivax***	**Effective against *P. falciparum* resistant to:**	**Cross-resistance**	**Cost (USD) per adult treatment course**
Chloroquine (CQ)	Yes		Hydroxy-CQ. Possibly AQ, PMT, QN	Tablets: 0.072 (0.062-0.08) Syrup: 0.85 (0.21-2.37) Injection: 0.54 (0.49-0.63)
Amodiaquine (AQ)	Yes	CQ (partially)	CQ	0.15
Sulfadoxine/pyrimethamine (SP)	No	CQ	Antifolates	0.082 (0.065-0.098)
Sulfalene/pyrimethamine (SLP)	No	CQ	Antifolates	0.28
Quinine (QN)	Active against sexual and asexual erythrocytic forms	CQ and SP (sometimes cross-resistance with CQ)	Mefloquine (rare; with 4-aminoquinolines); QN is generally effective against CQ and SP resistant malaria parasites	Tablets: 1.35 (1.22-1.63) Injection: 2.57 (2.21-3.0) (7 days)
Quinimax (a combination of QN, quinidine, cinchonine and cinchonidine)	As for QN	CQ and SP	Mefloquine	na*
Quinidine	As for QN	CQ and SP (sometimes cross-resistance with CQ)	Mefloquine	8.82
Mefloquine (15 mg/kg)	Yes	4-aminoquinolines and SP combinations	Halofantrine, reduced sensitivity to QN	2.14 (1.55-3.18)
Mefloquine (25 mg/kg)	Yes	As for mefloquine (15 mg/kg)	As for mefloquine (15 mg/kg)	3.22 (2.33-4.77)
Halofantrine	Yes	CQ, SP, QN	Mefloquine	Tablets: 4.75 Syrup: 0.28
Artemether	Yes	CQ, SP, QN		Tablets: 4.20 (China) Injection: 8.8 (China)
Artemisinin	Yes	CQ, SP, QN		Tablets: 2.10 (Vietnam)
Artesunate	Yes	CQ, SP, QN		2.16 (1.98-2.33) Injection: 11.2
Dihydroartemisinin	Yes	CQ, SP, QN		na
Artelinic acid	na			
Primaquine	Yes			Antirelapse: 0.06-0.24 (0.04-3.15)

Table 1.1: continued...

Option	Effective against *P. vivax*	Effective against *P. falciparum* resistant to:	Cross-resistance	Cost (USD) per adult treatment course
Doxycycline	No	Used in combination with QN in areas of reduced QN susceptibility		0.08-0.11 (0.06-0.21)
Tetracycline	Yes	Used in combination with QN in areas of reduced QN susceptibility		0.14-0.20 (0.12-0.25)
Proguanil	Yes		PMT	
Dapsone	No			
Atovaquone/proguanil	No	CQ, SP, halofantrine, mefloquine, AQ		42
Pyronaridine	No			
Quinine+doxycycline	Yes	QN alone	As for quinine and doxycycline	QN-sensitive areas, QN-3+D-3 0.63 (0.55-0.84) QN-resistant areas, QN-7+D-7 1.47 (1.3-1.66)
QN+tetracycline	Yes	QN alone	As for quinine and tetracycline	QN-sensitive areas, QN-3+T-5 0.79 (0.66-1.16) QN-resistant areas, QN-7+T-7 1.65 (1.42-2.27)
QN+SP	Yes	QN alone	As for QN and SP	0.66 (0.59-0.8)
Artesunate+mefloquine	Yes	CQ, SP, mefloquine	As for mefloquine	5.38 (4.06-7.04)
Artemisinin+mefloquine	Almost no data		As for mefloquine	
Artesunate+SP	Yes	CQ	As for SP	2.24 (2.05-2.43)
CQ+SP	Yes	CQ		0.154 (0.127-0.18)
CQ+SLP	Yes	CQ		0.35 (0.34-0.36)
Artemether+lumefantrine	No	CQ, SP	As for artemether	2.5
Dapsone-chlorproguanil	No	CQ, SP	Possibly other antifolates	Possibly <0.50
Dapsone-chlorproguanil/ artesunate	Yes	CQ, SP		na
Pyronaridine+artesunate	Yes	CQ, SP		na

*na-not available

The seemingly wide range of antimalarial drugs in Table 1.1, however, is tempered by economic realities on the African continent. Contemporary malaria chemotherapy in sub-Saharan Africa makes use of only a handful of antimalarial drugs (Winstanley *et al.*, 2004). Chloroquine (CQ) was used in many countries in sub-Saharan Africa as first-line drug until

recently and is still used extensively in parts of the continent. Amodiaquine (AQ), another 4-aminoquinoline, has similar properties to CQ. However, the drug's utility has been limited by concerns about its safety, specifically, agranulocytosis and acute hepatitis have been well-documented following use of AQ in prophylaxis (Hatton *et al.*, 1986; Larrey *et al.*, 1986; Neftel *et al.*, 1986; Rhodes *et al.*, 1986; WHO, 1987; Rouveix *et al.*, 1989; Phillips-Howard, 1990; Orrell *et al.*, 2001). Safety concerns have kept AQ off the WHO list of essential drugs until recently when a systematic review showed that the drug was not more toxic than sulfadoxine-pyrimethamine when used to treat uncomplicated malaria (Olliaro *et al.*, 1996).

Another class of antimalarial drugs with great utility in sub-Saharan Africa is the antifolate combinations. Sulfadoxine or sulfalene combined with pyrimethemine (SP) is the first-line drug in many countries, although resistance has emerged quite rapidly. Another antifolate combination that is more efficacious than SP and less prone to drug resistance is chlorproguanil-dapsone (Lapdap®). This drug became available in the last two years and its safety in routine use is being evaluated under the auspices of the WHO. Its utility however has been greatly limited following a push towards artemisinin-based combination therapy (ACT) in the continent, thus the drug is being combined with artesunate (chlorproguanil-dapsone-artesunate, CDA) to make it more attractive as a policy option in the fight against malaria. Quinine has been used for generations in Africa and throughout the world, especially as a reserve drug for complicated malaria. In most countries therefore, it is usually second- or third-line drug. In some countries like Kenya, oral quinine is used as second-line therapy for uncomplicated malaria, but symptomatic toxicity (e.g. "tinnitus", i.e. ringing sound in the ears) and a complicated dosing regimen (several doses a day for seven days) makes it impractical as an oral drug. Other antimalarial drugs which are less commonly used include mefloquine, halofantrine, atovaquone-proguanil and the antibiotic antimalarials such as doxycycline, tetracycline and clindamycin (Winstanley *et al.*, 2004).

ACTs are widely regarded as safe and highly efficacious and the way forward for malaria control in sub-Saharan Africa. The rationale for ACTs lies in the fact that the odds of a parasite developing resistance to two drugs in combination at the same time is considered to be very small, a principle which has been used effectively to confront other infectious diseases like tuberculosis and HIV/AIDS (White, 1999; White *et al.*, 1999; Nosten & Brasseur, 2002). However, ACTs pose an enormous cost challenge to already resource-constrained governments in sub-Saharan Africa (Bloland *et al.*, 2000; Snow *et al.*, 2003). Snow and colleagues (2003) estimate that between 1.6 and 3.4 billion US dollars are required to give Africa a chance to ensure a drug policy based on ACTs. It is envisaged that such funds will be paid for by the international donor community by way of funds availed through the Global Fund for AIDS, tuberculosis and malaria (GFATM). It is also envisaged that the cost burden of ACTs would be substantially reduced by targeting resources more effectively by for instance availing them free of charge only to at-risk populations like paediatric patients. Costs would still be reduced further by availing better diagnostic facilities (e.g. rapid diagnostic tests) for malaria (Snow *et al.*, 2003).

In its recently released seminal report entitled "Saving lives, buying time: economics of malaria drugs in an age of resistance", the United States Institute of Medicine (IOM) makes a similar observation about malaria therapy in Africa and the need for ACTs. The IOM notes that in the era of chloroquine resistance, the artemisinins are the only first-line antimalarial drugs appropriate for widespread use that still work against all chloroquine-resistant malaria parasites (IOM, 2004). Further, the report notes the relatively high cost of the artemisinins compared to failed or currently failing first-line antimalarial drugs, which are five to 10 times higher than CQ or SP, and recommends "...a sustained global subsidy of the artemisinins co-formulated with other antimalarial drugs (i.e. ACTs) as the most economically and biomedically sound means to meet the challenge of malaria".

1.7 Drug resistance

1.7.1 Definition and determinants

Drugs act by interfering with cellular or biochemical processes, often called targets. A classical target is the inhibition of enzymes necessary for parasite biochemical processes thus interfering with parasite growth. The antimalarial drug SP for instance acts by sequentially blocking two malaria parasite enzymes: dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) that are necessary for the synthesis of folic acid which is in turn used in the synthesis of purines, a precursor for amino acid synthesis. Drug resistance refers to the continued growth of a parasite in the presence of a standard dose of a drug to which it was previously sensitive. The drug or its metabolite selectively eliminates susceptible parasites and leaves parasites that have become resistant to it, i.e. mutants. Resistant parasites therefore multiply in the host and with time become the dominant parasite population (James & Gilles, 1985).

The main determinant of the length of the useful therapeutic life (UTL) of a drug is the pace of development of resistance. Hastings (2001) postulates that this pace depends on a number of factors: (i) the starting frequency of resistance; (ii) the level and pattern of drug use; (iii) the drug's pharmacokinetic properties; (iii) the number of genes required to encode resistance; (v) the level of sexual recombination in the parasite population; (vi) intra-host dynamics; (vii) the genetic basis of resistance; and (viii) the number of individual parasites in an infection.

1.7.2 The geography of antimalarial drug resistance

The spread of resistance to antimalarial drugs is best exemplified by that of *P. falciparum* to CQ. CQ-resistant *P. falciparum* was first reported in 1957 in the Thai-Cambodian border and soon after in Thailand. Resistance soon spread to South America (in 1960) and

to Papua New Guinea (in 1976). In Africa, confirmed cases of CQ-resistant infections were first reported in non-immune tourists to Kenya and Tanzania in 1978 and in semi-immune Kenyans in 1982. Resistance soon spread inland to countries such as Sudan, Uganda, Zambia, and to Malawi, leading to the view that resistance first spread from Southeast Asia to Africa because of population movements. This view has been confirmed by population genetics studies which have noted the similarities between African and Asian strains of CQ-resistant *P. falciparum* and their difference from those found in South America and Papua New Guinea (Talisuna *et al.*, 2004).

In contrast to resistance to CQ, which emerged slowly, that of *P. falciparum* to the antifolates emerged almost instantaneously. That to proguanil was noted in Malaya in 1947, one year after it was introduced. It is believed that resistance to pyrimethamine and cross-resistance to proguanil, chlorproguanil, and cycloguanil first emerged in Muheza, Tanzania in 1953 and spread slowly to northern Tanzania. SP was introduced in Thailand in 1967 and resistance was reported the same year. Resistance to mefloquine was reported in 1982, five years after its introduction while that to atovaquone was reported the same year it was introduced (1996). Resistance to the artemisinins has not been reported, although recrudescence among patients who have received a short course of therapy (i.e. less than 5 days) is not uncommon (Talisuna *et al.*, 2004).

1.7.3 Measurement of antimalarial drug resistance

Broadly, three methods are used to measure resistance to the antimalarial drugs: *in vivo* tests, *in vitro* tests, and molecular markers. *In vivo* tests involve the use of human subjects and parasitological and/or clinical markers as endpoints. Typically, patients are enrolled into the study, given the drug of interest, monitored over a given period, and assessed for response to the drug in terms of parasite clearance or clinical outcomes such as fever, or both. There has always been a great deal of controversy around the suitability of pure

parasitological or pure clinical definitions of efficacy/resistance leading the WHO to adopt both methods in its most recent definition of adequate clinical and parasitological response (ACPR, Table 1.2). Another controversy has been the number of days of follow-up (needed to differentiate true recrudescence from re-infection), this however has not been resolved satisfactorily in the literature and guidelines still give recommended follow-up periods ranging form 7 to 28 days for most antimalarial drugs (WHO, 1996; 2003a; Olliaro & Bloland, 2001).

Table 1.2: Definitions of antimalarial drug efficacy (WHO, 1996; 2003a)

Indicator	Definition
Early treatment failure (ETF)	Development of danger signs or severe malaria within the first three days (with parasitaemia) or a history of fever (axillary temperature ≥37.5°C) on Day 2 or 3 in the presence of parasitaemia. Parasitaemia on Day 3 ≥25% of the count on Day 0 on its own also qualifies as ETF
Late treatment failure (LTF)	Recorded if danger signs or severe malaria occur on Days 4 to 14 (with parasitaemia), or there is fever with parasitaemia on Days 4 to 14 without previously meeting criteria for ETF
Adequate clinical response (ACR)	Achieved if there is no parasitaemia or no fever on Day 14 without previously meeting the criteria for ETF or LTF
Late parasitological failure (LPF)	Presence of parasitaemia on Day 14 or 28 and axillary temperature < 37.5°C, without previously meeting criteria for ETF or LTF
Adequate clinical and parasitological response (ACPR)	Absence of parasitaemia on Day 14 (or Day 28), irrespective of axillary temperature, without previously meeting any of the criteria for ETF, LTF or LPF

In vitro tests involve obtaining samples from patients, which are then tested to estimate resistance patterns found among parasites circulating in a given area. They therefore reflect intrinsic parasite susceptibility to a given drug whereas *in vivo* tests demonstrate the interaction between parasite, drug, and host immune systems to effect a therapeutic response. Current *in vitro* tests include the WHO Mark II test, use of radio-labelled hypoxanthine, and the pLDH microtest. Use of molecular markers involves monitoring known mutations at certain points in the parasite genetic material and using this to predict the pattern and pace of development of antimalarial drug resistance. For example, it is

know that there is a correlation between increased frequency of mutations in DHFR (at codons 108, 51, 59, and 164) and DHPS (codons 436, 437, 540, 581, and 613) genes and SP resistance across the world. The utility of these methods however is limited by technical difficulties and a poor understanding of mechanisms of resistance for most antimalarial drugs (Olliaro & Bloland, 2001).

1.7.4 P. falciparum resistance to common antimalarial drugs and current first-line policies in sub-Saharan Africa

Table 1.3 shows countries in the WHO Africa Regional Office (AFRO) where *P. falciparum* is the predominant parasite in malaria infections. Algeria and Mauritius have been excluded from the table because the predominant parasite is *P. vivax* whose public health impact in Africa is negligible. The table demonstrates that the majority of countries in the AFRO region have reported resistance to CQ and the next favourite first-line drug, SP. Resistance to AQ is less common. In December 2004, most countries had changed to ACT, especially artesunate-AQ or artemether-lumefantrine (ART-LUM). However, 15 of these countries, including Kenya, had not yet implemented the new first-line policy.

Table 1.3: Antimalarial drug resistance to *P. falciparum* and current policy in the WHO Africa Regional Office (WHO AFRO*). Sources: Dr. Peter Olumese, WHO, personal communication and http://mosquito.who.int/amdp/amdp_afro.htm, accessed 20/12/04.

Country	Reported resistance to:			Current first line policy for presumptive diagnosis of uncomplicated malaria
	CQ	SP	AQ	
Angola	Yes	Yes	Yes	CQ
Benin	Yes	Yes	No	ART-LUM†
Botswana	Yes	No	No	SP
Burkina Faso	Yes	Yes	Yes	CQ
Burundi	Yes	Yes	No	AS-AQ
Cameroon	Yes	Yes	Yes	AS-AQ†
Cape Verde	na	na	na	CQ
Central African Republic	Yes	No	No	CQ
Chad	Yes	Yes	Yes	CQ
Comoros	Yes	Yes	No	ART-LUM†
Congo Brazzaville	Yes	No	No	CQ
Cote d'Ivoire	Yes	Yes	No	AQ or SP
Democratic Republic of Congo	Yes	Yes	No	SP
Equatorial Guinea	Yes	Yes	No	CQ
Eritrea	Yes	Yes	No	CQ+SP
Ethiopia	Yes	Yes	Yes	ART-LUM
Gabon	Yes	Yes	Yes	AS-AQ†
Gambia	Yes	No	No	CQ
Ghana	Yes	Yes	No	AS-AQ†
Guinea	Yes	No	No	CQ
Guinea-Bissau	Yes	No	No	CQ
Kenya	Yes	Yes	Yes	ART-LUM†
Liberia	Yes	No	Yes	AS-AQ†
Madagascar	Yes	No	No	AS-AQ†
Malawi	Yes	Yes	No	SP
Mali	Yes	Yes	No	ART-LUM†
Mauritania	Yes	No	No	CQ
Mozambique	Yes	Yes	Yes	AQ+SP
Namibia	Yes	Yes	No	ART-LUM†
Niger	Yes	No	No	CQ
Nigeria	Yes	Yes	Yes	CQ
Rwanda	Yes	Yes	No	AQ+SP
Sao Tome and Principe	na	na	na	AS-AQ†
Senegal	Yes	Yes	Yes	AQ+SP†
Sierra Leone	Yes	Yes	Yes	AS-AQ†
Somalia	Yes	Yes	No	na§
South Africa (Kwazulu Natal)	Yes	Yes	No	ART-LUM‡
South Africa (Mpumalanga)	Yes	Yes	No	AS+SP
Sudan	Yes	Yes	Yes	na
Swaziland	Yes	No	No	CQ
Togo	Yes	No	No	CQ
Uganda	Yes	Yes	Yes	ART-LUM†
United Republic of Tanzania	Yes	Yes	Yes	ART-LUM†
Zambia	Yes	Yes	No	ART-LUM
Zanzibar	Yes	Yes	Yes	AS+AQ
Zimbabwe	Yes	Yes	No	CQ+SP

*Algeria and Mauritius excluded because *P. vivax* predominates
† Policy adopted, not presently being deployed, implementation process on-going
‡ Laboratory confirmation of malaria required
§ na-not available

1.7.5 Public health impacts of drug resistance

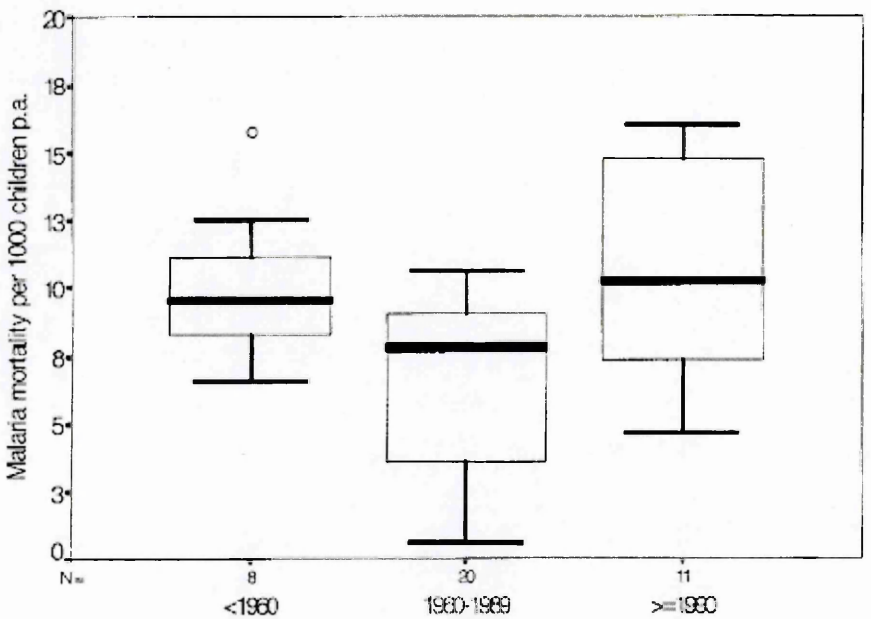
The public health implications of resistance to the antimalarial drugs are enormous. Antimalarial drug resistance leads to increase in malaria transmission in an area. Failure to clear parasites from patients means that more and more patients will carry resistant parasites in their blood, which in turn increases the biomass of resistance parasites in the population. Drug resistance also increases transmission by increasing gametocyte carriage in a given population as a result of longer parasite clearance times, which are associated with increased gametocyte carriage or increased frequency of recrudescent infections, which are twice as likely to carry gametocytes compared to primary infections (Olliaro & Bloland, 2001).

Furthermore, antimalarial drug resistance results in an increase in the frequency of severe malaria in the population since failing first-line drugs means patients will delay treatment and present to health facilities where second- and third-line drugs are mostly available when it is perhaps too late. Data from Malawi showed that in 1993, during the policy change from CQ to SP, hospital admissions due to uncomplicated malaria, anaemia and cerebral malaria had increased by 14%, 22% and 10%, respectively. The rates of anaemia and cerebral malaria however declined substantially after the policy change to SP, which was more efficacious at the time (Olliaro & Bloland, 2001).

Most significantly, antimalarial drug resistance results in increased mortality. Trape and colleagues (2002) demonstrate this aptly in a study in Mlomp, Senegal. In an area well catered for by an efficient health system run by catholic nuns, CQ was for a long time the mainstay therapy for malaria therapy. The authors show that following the emergence of CQ resistance in the early 90s, malaria mortality increased 11-fold among children 0-4 years old. In a review of trends in childhood mortality in Africa spanning several decades, Snow *et al.* (2001a) demonstrate that there was an increase in malaria-specific mortality in

Africa in the 1990s despite an overall decline in all-cause mortality (Figure 1.4). They postulate that the most plausible explanation for this was the concomitant precipitous decline in the clinical efficacy of CQ, which had been in use as a first-line drug across much of Africa at the time. Korenromp *et al.* (2003) show a similar rise in malaria-specific mortality in Africa in the 1990s, coincident with the precipitous decline in the clinical efficacy of CQ, using more robust statistical methods than previous work by Snow and colleagues'.

Figure 1.4: Trends in malaria-specific mortality in African children aged 0-4 years between 1912 and 1995 (Snow *et al.*, 2001a).

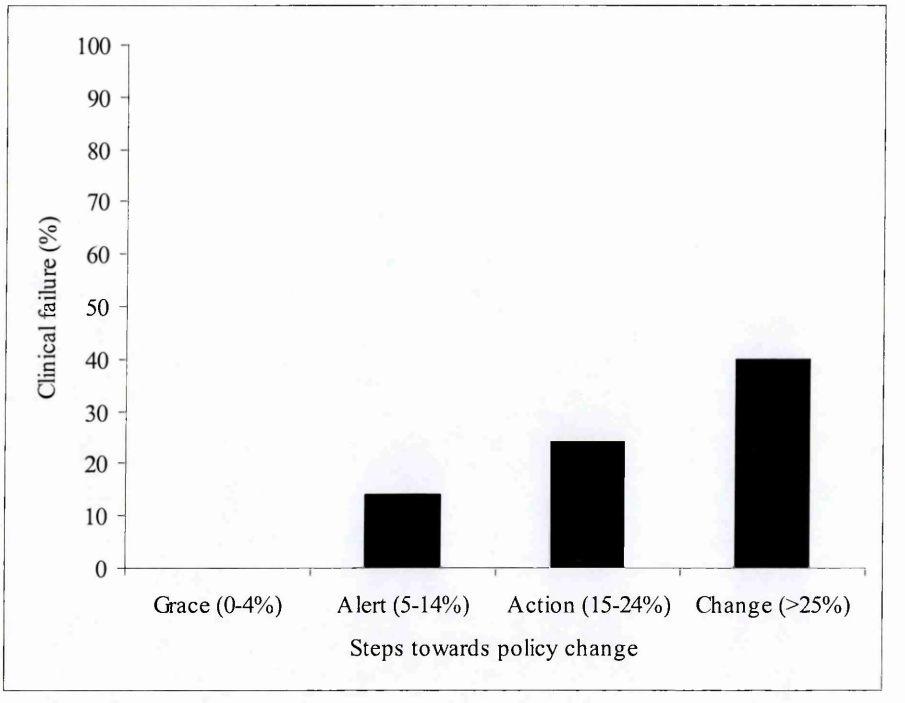


Failing first-line drugs means patients have to resort to increasingly expensive medications to self-treat and governments spend more in terms of hospitalisation costs and more importantly in changing first-line policies to more efficacious and invariably more expensive antimalarial drugs (for instance, 20 out of 45 countries in the WHO AFRO region have had to change first-line policy to ACTs in the last decade (http://mosquito.who.int/amdp/amdp_afro.htm, accessed 20/12/04; Table 1.3). A key issue

that has been debated is the stage at which it is economically viable for a country to change policy. This is a complex decision which involves trade-offs between competing alternatives (Goodman *et al.*, 2001) and is even more important in the advent of the ACTs which are several times the cost of failing first-line drugs like SP, but which are more efficacious.

The World Health Organisation (WHO) advises national drug policy makers to consider AM drugs fitting into the following efficacy Phases (using results from *in vivo* efficacy tests): 'grace', 'alert', 'action' and 'change'(WHO, 1996; 2003a; Kitua, 2000). During the period of 'grace', the parasite is maximally sensitive to the drug, and this period lasts until treatment failure rates reach 4%. The 'alert' phase represents a period of treatment failure rates between 5-14%. This is followed by the 'action' phase (15-24%), during which period WHO advises that changes to policy be planned. Lastly, WHO recommends initiation of policy change when treatment failure rates exceed 25% (Figure 1.5). Although this rubric for policy change has been suggested and is therefore not absolute, it has nonetheless proved to be a useful tool for first-line antimalarial drug policy changes in many malaria endemic African countries (EANMAT, 2003).

Figure 1.5: Phases of antimalarial drug policy change using the WHO efficacy model (WHO, 1996; 2003a)



1.8 Treatment seeking for fevers and malaria in sub-Saharan Africa

In many low and middle-income countries, public service providers provide health services to only a fraction of the population with most people obtaining their public health products[1] (PHPs, which include condoms, mosquito nets and antimalarial drugs), from a myriad of private service providers ranging from private medical clinics, pharmacists and their clerks, indigenous herbal practitioners, general provisions shops, mobile hawkers and licensed and unlicensed medicine shops. The lines are blurred between what constitutes formal or informal health service providers, licensed or unlicensed providers, and licit and illicit trade in PHPs. In some countries for instance, "medicine shops" are licensed and may legally sell proprietary, over-the-counter (OTC) drugs such as analgesics, cough syrups, vitamins, and a variety of antimalarials. In practice, however, these shops also often illegally sell injectable antimalarials, antibiotics, tranquillisers, and other prescription drugs. General

[1] Defined by Conteh & Hanson (2003) as "...commodities that are used for treatment of diseases of public health importance or for the promotion of health, which can be provided at the retail level without a 'service' attached to them".

provision shops usually do not qualify a license to sell even OTC drugs, but they often stock antimalarials and antipyretics and occasionally a limited range of prescription drugs (RBM, 2004). Further, while pharmacies are considered "formal" on paper since there are minimum *de jure* training and licensing requirements for staff, in practice most of them are only so in name since they are mostly run by assistants with little or no health-related training (Conteh & Hanson). Therefore, these lines can at best be said to be country specific.

Conteh & Hanson (2003) suggest three useful typologies that might be used to classify private providers of PHPs: commercial orientation (profit/not-for-profit), qualifications of staff (formal health-related training/little or no training) and organizational complexity (single hawker to multi-department institutions such as hospitals). In this thesis, a slight modification of the first two typologies is used within the context of each chapter. The term "formal" for instance is used to denote providers with formal, health-related training, for instance government clinics and hospitals, mission clinics and hospitals and doctors and nurses in private practice (Chapter 2). At times a distinction is made between providers within the "formal" sector by using their commercial orientation as a sub-typology; thus the terms "public formal" (meaning not-for-profit formal service providers) and "private formal" service providers (e.g. doctors and nurses in private practice). Public formal service providers are classified further in some chapters to see if there are any patterns in terms of community drug use or costs (Chapter 4).

There are two contexts in which the term "home" is used in the thesis: first is the treatment of fevers at home using western medications (Chapters 1 and 2). Some of the drugs used at home will already be in the household, left over from previous fever episodes, but most will be obtained from shops or pharmacies. Moreover, the use of western drugs already at home as a fever treatment action constitutes less than 4% of first actions (Chapter 4) and

these drugs would largely have been obtained from shops or pharmacies in a previous fever episode (Deming *et al.*, 1989; Marsh *et al.*, 1999; Molyneux *et al.*, 1999). Therefore, where the key distinction is between the use of western drugs at home and drugs obtained from formal providers, western drugs at home are put together with those obtained from the retail sector (the most likely source of drugs used at home). The term "home" also appears in Section 1.8.2 under the World Health Organization's home-based management of malaria (HMM). HMM is defined by WHO as "...early recognition of, and prompt and appropriate response (treatment) to malarial illness in children under 5 years of age in the home or community"(http://www.who.int/malaria/homemanagement.html) and would naturally include actions involving the use of the retail sector (which is the most common for fevers and malaria in Africa)". The term "retail" strictly denotes Conteh & Hanson's (2003) commercial orientation typology and is used to denote retail pharmacies, mobile drug vendors and general provision shops. Footnotes (for tables) and definitions in the text are used to remind the reader the context in which the terms are used throughout the thesis.

1.8.1 Literature review

As part of the present literature review, 48 studies across 17 countries in sub-Saharan Africa and one recent review were *selected* and these have been used to outline some basic features using medians of various categories of behaviour. No formal search strategy was used and therefore the coverage and completeness of the information obtained from these studies must be viewed with caution. Similar data for Kenya have not been included here because this is dealt with in more detail (and in context) in Chapter 2, which is Kenya-specific. The following account is based on an analysis of these studies.

The literature on treatment seeking for fevers and malaria in sub-Saharan Africa is copious. There are, however, a number of methodological difficulties in trying to compare these across time and studies to bring out generalisable patterns of behaviour. In a recent review,

McCombie (2002) observes that authors use a variety of methods of inquiry. Some use hypothetical questions such as 'how would you treat malaria or fever in your child or yourself', others ask about specific actions taken in response to fever or malaria. In addition, authors use different recall periods to define fever or malaria and definitions of treatment actions or terminologies used to elicit responses from interviewees are varied or simply not apparent. Regardless of these methodological challenges, a number of broad generalisations can be inferred.

1.8.1.1 Definition of fever

Communities use different terminologies to describe fever or malaria. Sometimes these definitions closely approximate the biomedical definitions of fever or malaria, but more commonly, they incorporate broader connotations of illness. In northern Ghana for instance, *pua* or *paa* are used to describe febrile illnesses including headaches, skin rashes, diarrhoea, and/or vomiting. When compared with biomedical definitions of malaria (raised body temperature and parasite density >=4,000/μl blood), the lay definition afforded a sensitivity of 42% and a specificity of 79% during the peak malaria season (Binka *et al.*, 1994). Similarly, in Uganda, lay definitions of malaria when compared with gold standard biomedical definitions afforded a sensitivity of 37% and a specificity of 58% (Lubanga *et al.*, 1997). In some communities, there are a number of illness categories and malaria may be divided into different types. Among the Dangme of Ghana, *asra* is used to denote fever, while *asraku* refers to a high fever (Agyepong & Manderson, 1994). Overall, local definitions of fever and malaria are poorly predictive of biomedical malaria.

1.8.1.2 Treatment of fevers

Treatment of fever and malaria is very high. Table 1.4 shows 48 studies conducted in 17 countries across sub-Saharan Africa between 1978 and 2002 (see Table 1.5 for summary statistics). From these studies, the majority of fevers were reportedly treated (median 96%,

interquartile range (IQR) 89%, 100%). For the same fever episode, multiple treatments are not uncommon; about a third of all fevers are treated from at least two sources (median 33%, IQR 11%, 43%). Most fevers are treated at home (median 51%, IQR 26%, 73%) or from the public or private sector clinics (median 49%, IQR 29%, 64%). Fevers treated at home mostly receive antipyretic (median 63%, IQR 60%, 79%) or antimalarial drugs (median 42%, IQR 28%, 57%). Fevers treated at public or private clinics are more likely to receive an antimalarial drug than are those treated at home (median of 73% versus 42%). Adherence to antimalarial drugs (dose and duration of treatment) is generally poor among populations in the continent (median 30%, IQR 11%, 37%).

1.8.1.3 Timing of treatment

From the literature, a delay in seeking treatment is common. In a study in Kabale, Uganda, Lindblade *et al.* (2000) report that over 80% of adults and children sought treatment on the day of illness or on the second day. However, Deressa *et al.* (2003a) report that over 60% of patients in Butajira district, Ethiopia sought treatment after 2 days of illness and in Shewa a delay of 3 days or greater was observed among the majority of children aged less than five who sought treatment (>75%). The main reasons for the delay were: perceived mildness of illness, high workload of guardians, financial problems or guardians thought they were dealing with another disease and not malaria (Deressa *et al.*, 2003b). Studies in Kenya report delay periods of two to three days (Chapters 2 and 4).

Table 1.4: Treatment seeking for fevers and malaria in 17 sub-Saharan African countries.

Location	Year of study	Age of patients (years)	% fevers where treatment sought	% fevers with >1 treatment source	% fevers managed at home*	% fevers managed through public and/or private health facilities†	% fevers where no action taken‡	% fevers given AP at home	% given AM at home	% given AM at public and/or private facility	% taking adequate AM dose§	Reference
Osudoku, Ghana	1992-1993	0-4	na	na	na	na	na	60	39	na	na	Agyepong & Manderson, (1994)
Lusaka, Copperbelt and Eastern Province, Zambia	1997	All	na	na	na	na	na	na	na	57	na	Barat *et al.*, (1999)
Latebiokorshie, Accra, Ghana	1998-1999	0-5	94	na	54	38	6	na	na	na	na	Biritwum *et al.*, (2000)
Chokor, Accra, Ghana	1998-1999	0-5	98	na	73	23	2	na	na	na	na	Biritwum *et al.*, (2000)
Banjul, The Gambia	1996	0.5-9	na	na	na	na	na	na	60	na	na	Bojang *et al.*, (1997)
Lagos, Nigeria	1998	0.5-5	97	na	51	51	3	na	na	na	na	Brieger *et al.*, (2001)
Farafenni, Kaur and Soma, The Gambia	na	0-4	na	na	na	76	na	60	8	54	31	Clarke *et al.*, (2003)
Conakry, Guinea	1986	0-4	84	39	79	43	16	na	37	64	36	Dabis *et al.*, (1989)
Rufiji, Tanzania	1999-2001	0-4	88	64	20	59	12	na	na	na	na	De Savigny *et al.*, (2004)
Plateaux region, Togo	1984	0-4	92	11	83	20	na	na	na	na	30	Deming *et al.*, (1989)
Butajira, Ethiopia	1999	All	100		19	47	na	na	na	na	na	Deressa *et al.*, (2003a)
Shewa, Ethiopia	2000	15+	100	na	13	87	0	na	na	na	na	Deressa *et al.*, (2003b)

Table 1.4: continued...

Location	Year of study	Age of patients (years)	% fevers where treatment sought	% fevers with >1 treatment source	% fevers managed at home*	% fevers managed through public and/or private health facilities†	% fevers where no action taken‡	% fevers given AP at home	% given AM at home	% given AM at public and/or private facility	% taking adequate AM dose§	Reference
Maferinyah, Guinea	1996	0-4	65	na	19	14	35	na	na	na	na	Diallo *et al.* (2001)
Aboh Mbaise, Nigeria	1988	0.5-4	na	na	70	30	na	na	na	100	24	Ejezie *et al.*, (1990)
Nationwide, Malawi	1992	0-10	na	na	53	56	9	na	na	na		Ettling *et al.*, (1994)
Kilombero, Tanzania	1995-1996	All	na	na	na	na	na	na	na	73	na	Font *et al.*, (2001)
Bomi & Grand Cape, Liberia	1988	0-5	na	na	74	23	na	na	na	na	na	Foster *et al.*, (1993)
Berekuso, Ghana	1978	All	na	na	94	na	na	na	na	na	na	Gardiner *et al.*, (1984)
Telimele and Kindia, Guinea	na	0-5	na	na	na	33	na	na	na	na	na	Glik *et al.*, (1989)
Farafenni, The Gambia	1982-1984	0-7	64	na	na	na	36	na	na	na	na	Greenwood *et al.*, (1987)
Blantyre, Malawi	2000	0-4	97	33	39	25	3	63	12	na	42	Holtz *et al.*, (2003)
Naga-Eboko, Cameroon	1987	0-14	na	na	69	na	na	na	na	na	7	Josse *et al.*, (1988)
Yaounde, Cameroon	1987	0-14	na	na	91	na	na	na	na	na	20	Josse *et al.*, (1988)
Edea, Cameroon	1987	0-14	na	na	93	na	na	na	na	na	8	Josse *et al.*, (1988)
Tougan, Nouna, and Solenza, Burkina Faso	1994	0-4	na	na	44	27	na	na	na	98	na	Krause & Sauerborn, (2000)
Kabale, Uganda	1998	0-4	100	28	26	62	0	na	na	na	na	Lindblade *et al.*, (2000)

Table 1.4: continued...

Location	Year of study	Age of patients (years)	% fevers where treatment sought	% fevers with >1 treatment source	% fevers managed at home*	% fevers managed through public and/or private health facilities†	% fevers where no action taken‡	% fevers given AP at home	% given AM at home	% given AM at public and/or private facility	% taking adequate AM dose§	Reference
Kabale, Uganda	1998	15+	100	43	27	65	0	na	na	na	na	Lindblade *et al.*, (2000)
Yaounde, Cameroon	1990	All	90	na	36	54	10	na	na	na	na	Louis *et al.*, (1992)
Kampala, Uganda	1992	0-4	na	na	90	na	na	42	50	na	na	Lubanga *et al.*, (1997)
Katabas, The Gambia	1986	0-9	na	na	na	na	na	79	na	na	73	Menon *et al.*, (1988)
Dar es Salaam, Tanzania	na	na	na	na	72	7	na	na	na	na	na	Mnyika *et al.*, (1995)
Nouna, Burkina Faso	1999	0.5-3	85	na	na	na	na	na	na	na	na	Muller *et al.*, (2003)
Hoima, Uganda	na	Pregnant women	96	na	33	61	4	na	na	na	na	Ndyomugyenyi *et al.*, (1998)
Bagamoyo, Tanzania	1983-1984	0-4	95	na	18	85	6	na	na	na	na	Neuvians *et al.*, (1988)
Tororo and Busia, Uganda	1998	0-4	na	na	na	na	na	na	na	na	38	Nshakira *et al.*, (2002)
Udi LGA, Nigeria	1996-1997	0-4	na	na	na	na	na	na	na	na	36	Okonkwo *et al.*, (2001)
Imesi-ile, Nigeria	1990-1991	Adolescents	na	na	7	79	na	na	na	na	na	Okonofua *et al.*, (1992)
Accra, Ghana	1990	All	na	na	na	na	na	94	78	na	na	Osei & Beecham, (1990)
Sourou, Burkina Faso	1994-1995	0-4	na	na	na	na	na	na	na	na	3	Pagnoni *et al.*, (1997)

Table 1.4: continued...

Location	Year of study	Age of patients (years)	% fevers where treatment sought	% fevers with >1 treatment source	% fevers managed at home*	% fevers managed through public and/or private health facilities†	% fevers where no action taken‡	% fevers given AP at home	% given AM at home	% given AM at public and/or private facility	% taking adequate AM dose§	Reference
Idere, Mbaugwu, and Ukehe, Nigeria	1999	0.5-6	96	na	47	32	4	na	na	na	na	Salako *et al.*, (2001)
Maputo, Mozambique	1990	0.5-7	na	na	na	na	na	na	45	na	na	Schapira *et al.*, (1993a)
Gondar, Ethiopia	na	0-4	na	na	na	na	na	na	na	95	na	Simoes *et al.*, (1997)
Nationwide, Malawi	1992	0-9	na	na	na	54	na	69	56	74	14	Slutsker *et al.*, (1994)
Magochi, Malawi	1992	0-2	na	na	na	63	na	na	na	na	na	Slutsker *et al.*, (1996)
Harare, Zimbabawe	na	All	na	na	na	na	na	na	na	na	25	Stein *et al.*, (1988)
Yanfolila, Mali	1998	1-5	na	na	na	na	na	na	na	na	34	Thera *et al.*, (2000)
Kingandu, Democratic Republic of Congo	1984-1989	0-6	na	na	55	45	0	na	33	59	na	Vernon *et al.*, (1993)
Bougouni, Mali	2001-2002	0-6	na	na	na	na	na	na	na	na	1.5	Winch *et al.*, (2003)
Jimma, Ethiopia	2000	All	100	na	30	67	0	na	na	na	na	Worku & Gabremiriam, (2003)
Dar es Salaam, Tanzania	1993	0-4	100	na	20	84	6	na	na	na	na	Wyss *et al.*, (1996)
Wenchi, Ghana	1996	All	na	na	na	na	na	na	na	na	50	Yeboah-Antwi *et al.*, (2001)
Shoa, Ethiopia	1991-1992	0-10	100	0	58	41	na	na	na	na	na	Yeneneh *et al.*, (1993)

* Home-drugs at home or obtained from shops, pharmacies, drug vendors
† Public not-for-profit and private-for-profit facilities
‡ No action implies fever not treated or prayers used
§ Adequate dose of AM as defined by study
NA means not applicable or not provided

Table 1.5: Summary statistics for treatment seeking for fevers and malaria in 17 sub-Saharan African countries.

Indicator	Number of studies	Median	25% percentile	75% percentile	Minimum	Maximum
Percent fevers treated	21	96	89	100	64	100
Percent fevers treated from >1 source	7	33	11	43	0	64
Percent fevers treated at home*	31	51	26	73	7	94
Percent fevers treated at public and/or private clinic†	30	49	29	64	7	87
Percent fevers with no treatment‡	19	4	0	10	0	36
Percent fevers where antipyretic administered at home	7	63	60	79	42	94
Percent fevers where antimalarial administered at home	10	42	28	57	8	78
Percent fevers where antimalarial administered at clinic	9	73	58	97	54	100
Percent adherence to antimalarial dosage§	17	30	11	37	2	73

* Home-drugs at home or obtained from shops, pharmacies, drug vendors
† Public not-for-profit and private-for-profit facilities
‡ No action implies fever not treated or prayers used
§ Adequate dose of AM as defined by study

1.8.2 Promotion of home-based management of fevers and malaria by WHO

Because of the importance of private service providers (including the retail sector) in providing prompt access to drugs for fever and malaria (mostly antipyretic and antimalarial drugs), WHO has recognised the role of this sector in helping to meet international targets on access to antimalarial drugs, chiefly RBM's target of making sure the majority of children receive prompt, effective treatment for malaria within 24 hours. To this end, WHO has put forward four strategies to correct the common inadequacies of service provision in this sector (http://mosquito.who.int, accessed 20/12/04). These four strategies are:

1. Ensure access to effective and good quality antimalarial drugs (preferably pre-packaged) at the community level
2. Ensure that community drug or service providers have the necessary skills and knowledge to manage malarial illness (fever)
3. Ensure an effective communication strategy to enable caretakers recognise malaria illness early and take an appropriate action
4. Ensure a good mechanism for the supervision and monitoring of community activities

These strategies have largely been informed by lessons learnt from pilot research projects on the delivery of antimalarial services in many countries in Africa and plans are underway to scale them up to the national level in several countries including Kenya (WHO, 2003b).

1.9 Drug quality

It is important to consider the quality of drugs because of the intuitive link between drug quality and drug resistance. Sub-standard and counterfeit drugs could have either of two outcomes for therapeutics: a) they avail too much drug to the body (high content and dissolution scores, see Chapter 6) thus precipitating toxic or adverse reactions, or b) avail too little (low content and dissolution scores) resulting in sub-therapeutic levels of the drug

in plasma. Drug action is such that a minimum concentration is required to elicit a physiological response (lowering of blood pressure in hypertension for instance) or parasite kill in the case of malaria and other infectious diseases. The link between sub-therapeutic levels of antimalarial drugs and antimalarial drug resistance is usually explained in terms of "selection pressure" in the literature, i.e. low levels of a drug selectively kill susceptible parasites, leaving resistant parasites to flourish in their stead (sustained and haphazard use of drugs has the same effect). This is especially true for drugs with long half-lives (such as SP) and which therefore are more likely to spend part of their time in the body below the minimum inhibitory concentration required for parasite kill. This residual and sub-therapeutic drug in the host is likely to encounter re-infecting parasites, a common feature in areas of high transmission (most of sub-Saharan Africa), resulting in selective kill of susceptible parasites (Watkins & Mosobo, 1993; Nzila *et al.*, 2000).

Concern about the quality of drugs dates back to antiquity. As early as the fourth century BC, people were warned about the dangers of adulterated medicines, and despite all the advances made over the years, this concern is still apparent (WHO, 1999a). Although global standards for drug quality are becoming increasingly rigorous, the quality of drugs on the market in many countries, especially the developing ones, remains a major public health concern (WHO, 1999b; Newton *et al.*, 2001). The quality of antimalarial drugs is no exception and is part of the wider drug quality problem in developing countries.

1.9.1 Southeast Asia and Latin America

In Southeast Asia, Newton *et al.* (2001) investigated the distribution of counterfeit artesunate tablets. Of 104 shop-bought "artesunate" samples from Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, 38% did not contain artesunate. Characteristics such as the cost and physical appearance of the tablets and packaging reliably predicted authenticity. In an earlier study in Cambodia, a total of 242 vendors and pharmacies were

mapped in 12 market places, and 133 of these selected at random for investigation. In this study, fake artesunate was sold by 71% and fake mefloquine by 60%. Patients and village health providers frequently bought the fakes because of the lower price (Rozendaal, 2001).

In a study in the Amazonian region, Petralanda (1995) found that of 12 samples of primaquine (PQ) submitted for analysis to an independent laboratory, 50% failed to comply with the United States Pharmacopoeia (USP) qualitative requirements. None conformed to the USP quantitative requirements. A third of the samples analysed using the British Pharmacopoeia (BP) qualitative criteria failed.

1.9.2 Africa

In a recent study in Nigeria, for all groups of drugs investigated, more than 50% failed to comply with the BP specifications. Some preparations contained no active ingredient; some had too much and others too little. To illustrate two extremes, whereas all 19 proguanil tablet samples analysed complied with the BP specifications, all 20-chloroquine phosphate syrup samples failed to do so. For the other antimalarial drugs, pooled data for the active ingredients (regardless of type of salt or formulation) shows an average failure rate of 8% for quinine (QN) and 22% for SP (Taylor *et al.*, 2001).

Similar concerns about drug quality have been raised in Tanzania. In a recent study investigating the quality of nine brands of SP drugs marketed in Dar es Salaam, only four passed dissolution (an *in vitro* test for bioavailability) although all nine samples were within the limits for content of the active ingredients (Jande *et al.*, 2000). During screening tests for CQ intake in patients, Abdi *et al.* (1995) encountered one patient who tested negative for CQ, although she claimed to have taken CQ only 2 days earlier. This observation together with reports of poor quality of drugs elsewhere in Africa prompted

them to conduct a quality survey on nine CQ brands in Dar es Salaam. Although all brands passed tests for CQ content, a sugar coated brand failed dissolution.

A study in Uganda demonstrated problems with quality of CQ in the market. Up to 30% of the tablet samples and 33% of injections contained less than the stated amount of CQ (Ogwal-Okeng *et al.*, 1998). A number of studies, both published and unpublished have been done on the quality of antimalarial drugs in Kenya. Analysis of pooled unpublished data from two quality control (QC) laboratories (National Quality Control Laboratory (NQCL) and Mission for Essential Drugs & Supplies (MEDS) between 1998 and 2001 showed an average failure rate of 13.8% for AQ and 41.9% for SP products[2]. Further data from the NQCL showed a failure rate of 26.7% for CQ and 30% for QN. Too little, too much, or complete absence of the active ingredient has been noted amongst test failures. The active ingredient was sometimes substituted with a closely related (for instance sulphamethoxypyrazine with sulphamethoxypyridazine) or unrelated one (sulphamethoxypyrazine with paracetamol). Other problems included poor dissolution profiles, inadequate labelling, and faulty packaging.

The findings of a third QC laboratory (Drug Analysis and Research Unit (DARU) are summarised in Table 1.6 and demonstrate that the quality of antimalarial drugs in Kenya is highly variable. Most SP drugs tend to fail the dissolution test, especially with regard to the pyrimethamine component. However, QC results from the three laboratories need to be interpreted with caution since they are likely to be skewed. This is because analyses are done on samples submitted to the laboratories by a wide variety of clients, from those who suspect that the product of interest is of poor quality (e.g. in medico-legal cases) to those who seek first-time registration for a new product intended for the Kenyan market (Maitai

[2] Data provided by Dr. Sarah Chuchu on 141 tests conducted between 1996 and 2001 on AM samples submitted to NQCL. Dr. Jane Masiga provided the unpublished, anonymous data from 103 tests undertaken by MEDS between 1998 and February 2001

et al., 1982; Ogeto *et al.*, 1983; Kibwage *et al.*, 1992; 1999; Mang'era *et al.*, 1992; Vugigi *et al.*, 1997; Kibwage & Ngugi, 2000; Thoithi *et al.*, 2002).

Table 1.6: Antimalarial drugs analysed over the years at the University of Nairobi's Drug Analysis and Research Unit (DARU)

Study	AM drug	Number of requests for analysis	Number which failed
Maitai *et al.*, (1982)	CQ	1	1
Ogeto *et al.*, (1983)	CQ	6	1
	PQ	1	0
Kibwage *et al.*, (1992)	AQ	1	0
	CQ	11	0
	PQ	1	0
Mang'era *et al.*, (1992)	AQ	1	0
	CQ	4	0
Vugigi *et al.*, (1997)	SP	1	1
	CQ	21	3
Kibwage *et al.*, (1999)	SP	3	0
	AQ	1	1
	CQ	13	0
Kibwage & Ngugi, (2000)	SP	33	21
Thoithi *et al.*, (2002)	AQ	2	0
	CQ	30	4
	SP	45	18
	QN	4	0

1.10 Scope and role of the current thesis

Despite the importance of ITN in reducing morbidity and mortality due to malaria, the cornerstone of contemporary malaria control remains appropriate case management of febrile events. Case management is a key pillar of the RBM initiative and of the Kenya National Malaria Strategy and relies on the provision of safe, efficacious antimalarial drugs of adequate quality as close to home (or as early) as possible. In addition to ensuring that antimalarial drugs are safe, efficacious, and produced to the highest possible quality,

antimalarial drugs, need to be used rationally. Prompt treatment of malaria is especially important in children where the progression from mild to severe symptoms is rapid, resulting in potentially fatal severe malaria.

A key finding which runs through studies of treatment seeking for fevers and malaria in sub-Saharan Africa is the dependence on the retail sector for antimalarial and antipyretic drugs, which are often accessed as first-line drugs in the management of febrile events (Table 1.5). Despite the obvious significance of the retail sector, there has been, until recently, very little interest in it. This state of affairs may be attributed to the view that governments in sub-Saharan Africa have very little resources to regulate the retail sector and have largely adopted a *laissez faire* attitude. The WHO now recognises the importance of the private service providers (including the retail sector) and has begun to redress the deficiencies in our knowledge of this service sector (Section 1.8.2), but there remains a dearth of information on the potential of this sector to deliver quality services. This thesis addresses this research gap and aims to explore the potential of the retail sector in antimalarial service delivery by investigating the *Range, quality, and costs of antimalarial drugs available in the retail sector in Kenya.*

The thesis addresses a series of linked issues related to effective drug use by communities in Kenya. First, the national historical, political, and economic context is presented against the ever-changing status of antimalarial drug sensitivities (Chapter 2). This chapter provides a description of the complexities of drug use in Kenya and the political and financial frameworks that determine effective drug policy change. Chapter 3 considers the efficiency of the legislative and regulatory mechanisms in Kenya that are required to control rational drug use at a national level.

Chapter 4[3] presents the findings of a large community survey of paediatric fever treatment undertaken as part of the thesis in four districts. This work provides a contemporary (2001) series of findings related to sources, types, timing, and costs of treatment - all cornerstones of effective case-management strategies for RBM and the KNMS, with particular reference to the retail sector. Chapter 5 reports on a separate survey data to characterise the Kenyan retail sector in the same four study districts. It looks at the availability and affordability of antimalarial drugs and that of malaria preventative measures and explores shopkeeper knowledge of dosing for malaria with a view to understanding the limitations of the retail sector in antimalarial service delivery. Although there have been several reports of sub-standard and counterfeit drugs circulating in the market in Kenya, sampling of drugs for quality control (QC) has been focussed on major towns and cities or for the process of registration; there have been few district-level definitions of truly randomly sampled product ranges and QC of anti-malarial products. Chapter 6 presents the quality of first and second-line antimalarial drugs sampled during the retail surveys to overcome methodological deficiencies of previous studies.

Chapter 7[4] demonstrates the difference between the effectiveness and efficacy of antimalarial drugs using a quantifiable and multiplicative linear model of effectiveness. Whereas clinical efficacy trials (on which drug policy changes are based) are conducted in controlled environments with carefully supervised dosing schedules using quality-assured antimalarial products, in Kenya and in Africa, real-life evidence suggests that the quality of antimalarial drugs and adherence to dosage regimen is highly variable. The thesis aims to explore a number of key issues related to effective drug use in Kenya to better understand the differences between efficacy and effectiveness of antimalarial drugs and how these

[3] A digest of Chapter 4 has been published in Tropical Medicine and International Health, see details in bibliography under Amin *et al.* (2003).
[4] A digest of Chapter 7 has been published in Tropical Medicine and International Health, see details in bibliography under Amin *et al.* (2004).

might be used to redress deficiencies in national policy and legislation in Kenya. Finally, Chapter 8 pulls together the collective understanding of antimalarial drug use, quality and effectiveness in the context of Kenya's complex drug policy and legislative framework to propose a number of areas requiring further attention, strengthening and prioritising to maximise the use of new, expensive drugs in Kenya.

The main objective of the thesis was to examine the spectrum of antimalarial drugs available through the retail sector in Kenya against variations in costs, quality and drug use and the specific objectives were as follows:

1. Develop a national database of antimalarial products, registration status, and costs.
2. Track the process of registering AM products in Kenya using tracer drugs against existing defined procedures by way of documentary reviews and interviews with key informants.
3. Define the community usage patterns of antimalarial drugs in the management of fevers from formal and retail sectors in four districts in Kenya.
4. Undertake a retail audit assessment (range, costs, packaging and storage) of antimalarial products available in rural and urban communities of four districts in Kenya.
5. Perform quality tests on frequently stocked antimalarial drugs in the Kenyan retail sector using standard QC techniques.
6. Demonstrate the difference between effectiveness and efficacy of SP and AQ in Kenya and explore how these might be used to redress deficiencies in national policy and legislation
7. Inform policy regarding the introduction of new antimalarial drugs and to increase the community effectiveness of the national antimalarial drug policy

The thesis therefore used an eclectic mix of research methods to tackle a range of issues from policy review to pharmaceutical drug quality and mathematical modelling. The policy and legislative reviews in Chapter 2 and 3 used a mixture of documentary sources and key informant interviews and were entirely my responsibility. The community survey of 2001 was a concerted effort by the KEMRI/Wellcome Trust team in Nairobi (of which I am

part). The main aim of the bigger survey was to monitor progress towards targets set in the KNMS on various aspects of malaria in Kenya. Nested within this survey was a module on childhood fever management practices for which I was responsible and on which Chapter 4 is based. I designed the survey tools, piloted them, and was responsible for supervision of fieldworkers and quality assurance of collected data. Some work from other modules (use of ITN and intermittent presumptive treatment among pregnant women) has been published by colleagues (Guyatt *et al.*, 2004). The retail audit was split in two parts: a preliminary study where details on outlets were collected and antimalarial drug products were sampled for quality control (Chapter 6) and a more thorough review of range and costs of products (Chapter 5). I undertook the preliminary survey in the four study districts; I also trained and supervised field workers in the main survey. I was assisted in the quality control work by NQCL and MEDS and actively took part in the analysis of drug samples. Data on adherence for Chapter 7 were obtained from my colleague in Kilifi, Vicki Marsh, and the mathematical modelling of pooled data to estimate antimalarial drug effectiveness for the chapter were skills learnt whilst in Liverpool for which I am grateful to Dr Dyfrig Hughes.

CHAPTER 2:

Kenyan health sector, malaria, and background to thesis

2.1 Introduction

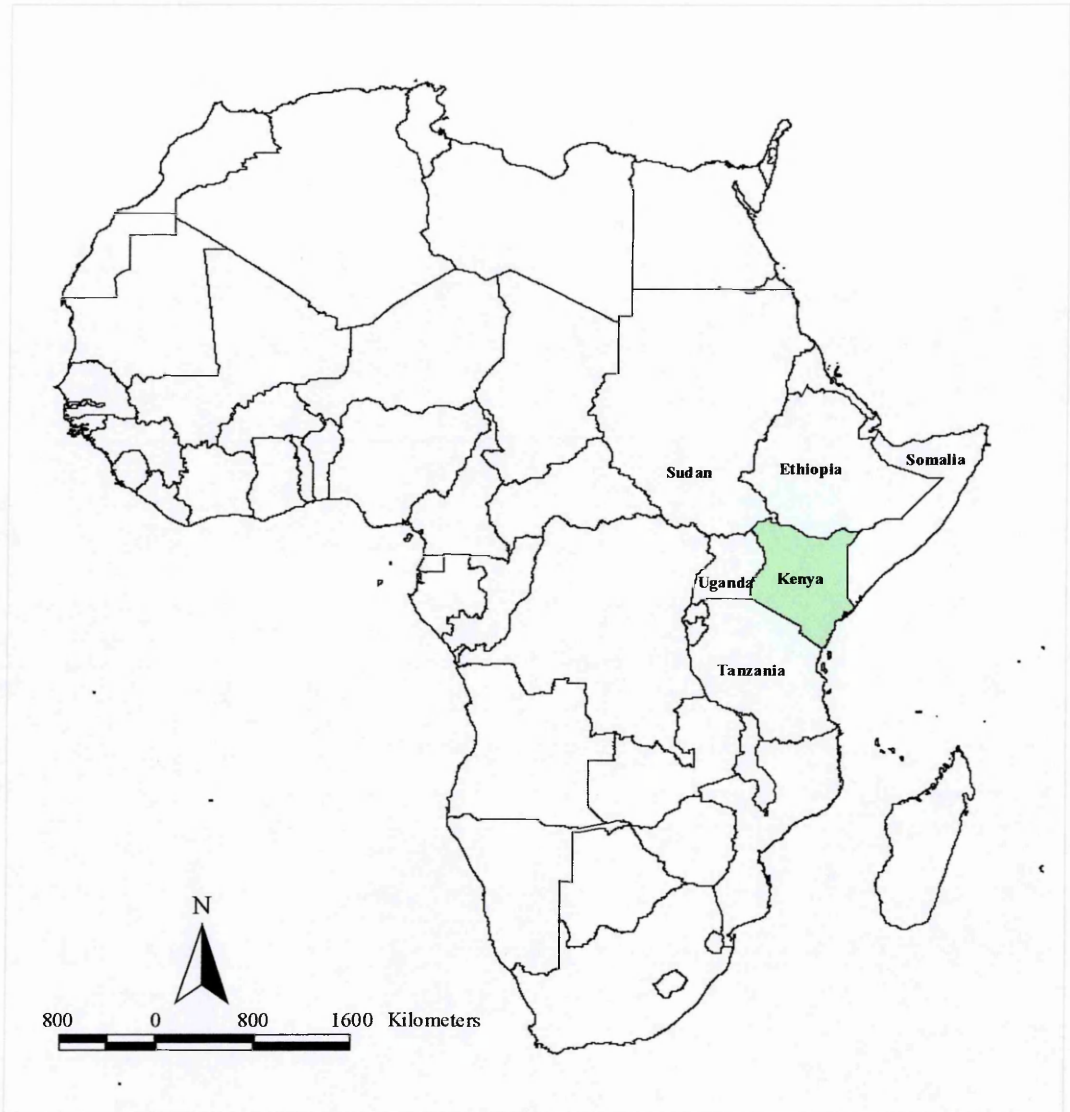
This chapter seeks to lay out the country context for the thesis. It begins by a general description of Kenya, the organisation of the Kenyan health sector and aspects of health sector reform that affect access to health care services. It then moves on to other drug specific issues including treatment seeking for fevers, drug resistance, drug efficacy, and anti-malarial drug policy. A description of historical antimalarial drug policy changes in Kenya, the current situation with artemisinin-based combination therapies (ACTs), and the political issues affecting drug policy changes in Kenya are then presented. The latter was particularly important given the transition in national drug policy during the period of the thesis, a dynamic event hopefully captured up to the period of completion of this thesis in December 2004.

2.2 Kenya

2.2.1 Location and basic indicators

Kenya is located in East Africa and shares borders with Uganda to the west, Tanzania to the south, Ethiopia to the north, Sudan to the northwest and Somalia to the east. Kenya is also bordered to the southeast by the Indian Ocean on which is located the port of Mombasa, the second largest city in Kenya (after the capital Nairobi) and an important gateway for trade in Kenya and the landlocked countries in the Great Lakes region to the west. The country lies approximately between latitudes 5°00'N and 4°40'S, and between longitudes 33°83'E and 41°76'E. Kenya is approximately 580,367 km^2 in area (Ojany & Ogendo, 1988).

Figure 2.1: Map of Africa showing the location of Kenya

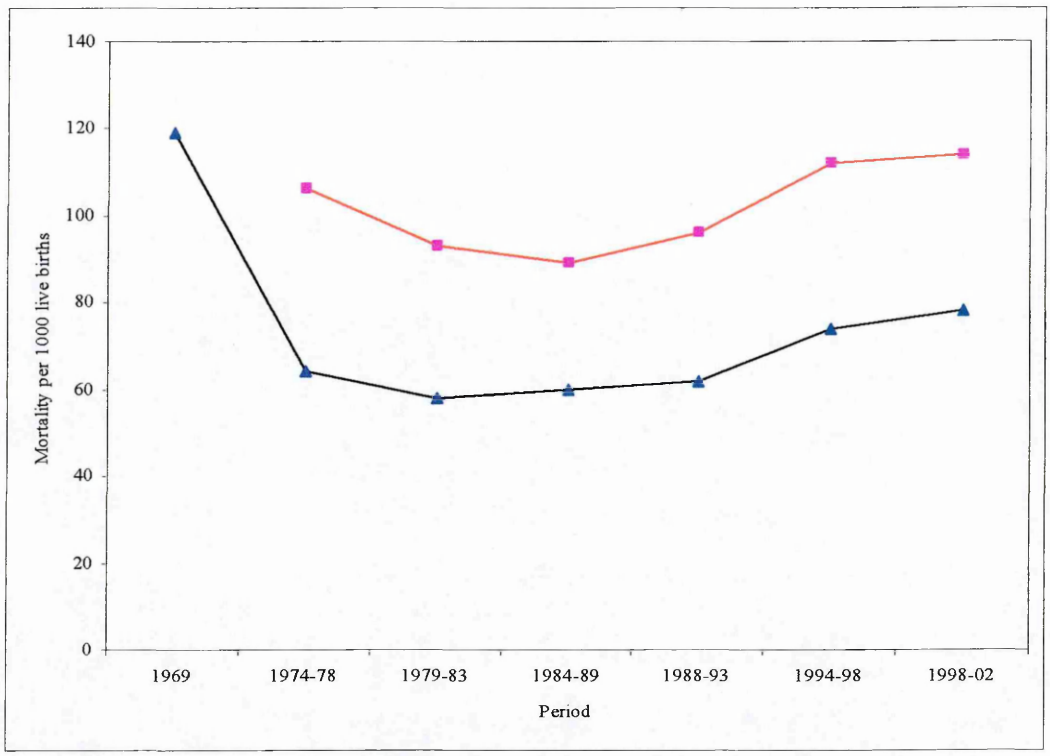


The country is divided into five administrative levels for purposes of local government, resource allocation (including education and health) and population census. There are eight provinces (first-level), which are further sub-divided into 70 districts (second-level). Districts are further sub-divided into divisions, locations, and sub-locations (third, fourth and fifth-level, respectively). The last National Population and Housing Census was carried out in 1999, the fourth since independence. The country's population was approximately 29 million persons in 1999, with most people living in the densely populated areas of Nairobi, the Coast and Western provinces of the country. Like most

developing countries, Kenya's population is predominantly young, during the 1999 census, 44% of Kenyans were aged below 15 years, 52% were aged between 15 and 64 years and 4% were aged 65 years and above (CBS, 2001a).

The general trend in the health status of Kenya's population was characterised by steady improvements from independence in 1963 until the early 1980s, this trend slowed in the mid 1980s and there followed a rapid decline during the 1990s. At independence, life expectancy at birth was 40 years (MoH, 2004a). This increased to 49 years by 1969 and to 58 years by 1979 (Owino, 1997). There was a marginal increase in life-expectancy to 60 years between 1979 and 1989 (Owino, 1997). However, life expectancy at birth dropped to 48 years by 1999 (CBS, 2001a). Childhood mortality indicators show a similar trend (Figure 2.2): infant mortality rates had been halved by the mid 1980s; from 119 in 1969 (MoH, 2004a) to 60 in the period 1984 to 1989 (NCPD, 1994). Likewise, in the same period, mortality among children under five years of age (per 1,000 live births) had dropped to 89 (NCPD, 1994). Both indicators show evidence of an increase by the early 1990s (NCPD, 1989; 1994; 1999; CBS, 2003).

Figure 2.2: Trends in infant* (dark blue line) and under five mortality† (red line) in Kenya between 1969 and 2002 (NCPD, 1989; 1994; 1999; CBS, 2003; MoH, 2004a).



* Probability (per 1,000 live births) of dying before the first birthday.
† Probability (per 1,000 live births) of dying between birth and fifth birthday.

In terms of economic development, Kenya's economy has been on the decline since the early 1990s. The total output of goods and services for final use produced by the Kenyan economy (Gross Domestic Product per capita) in 2000 was approximately Kenya Shillings (KES) 22,943 (US Dollars [USD] 316). Between 1996 and 1999, GDP growth plummeted from 4.6% to 1.4%. A negative growth of 0.3% was registered in the year 2000 (CBS, 2001b). Further, Kenya has one of the world's highest wealth disparities, with the poorest 10% of the population consuming only 1.8% of national income and the wealthiest 10% consuming 34.9%. In addition, almost half the population live below the national poverty line (World Bank, 2002). Efforts have been made to redress the situation: the Kenya government undertook a broad-based, consultative process in all districts of the country which resulted in the adoption of a "pro-poor" and "pro-growth" Poverty Reduction

Strategy Paper which proposes to reverse economic decline and reduce poverty levels by half by 2015 (GoK, 2001).

2.2.2 Organisation of the Kenyan health system

Health services in Kenya are provided by the government, partners in development like non-governmental organisations (NGOs), the mission sector, and the private sector. The government sector, which comprises Ministry of Health (MoH) facilities and facilities run by the Ministry of Local Government (in large municipalities, e.g. Nairobi), together with the NGO and mission sectors, are essentially non-profit making. Conversely, private-for-profit practitioners, clinics and hospitals provide curative and preventative services to those who can afford them (Owino, 1997).

The Government of Kenya (GoK) health care delivery system is organised according to three tiers, namely, the MoH headquarters in Nairobi, the provinces and the districts. At headquarters, the ministry is headed by a minister who is a political appointee assisted by two assistant ministers, a permanent secretary (PS) and a director of medical services (DMS). The PS plays an administrative role while the DMS's responsibility is largely technical. The MoH is further divided into a number of divisions with different responsibilities (Figure 2.3). The Division of Malaria Control (DOMC) for instance is the operational arm (i.e. executes decisions) of the National Malaria Control Programme (NMCP) and is responsible for overseeing the implementation of the Kenya National Malaria Strategy (KNMS).

The provincial tier acts as an intermediary between headquarters and the districts and is responsible for the implementation of health policy at the district level. It also maintains quality standards and coordinates and controls all district health activities. In addition, it monitors and supervises district health management boards (DHMBs) that oversee the

operations of health activities at the district level. The district level concentrates on the delivery of health services and generates their own expenditure plans and budget requirements based on guidelines from headquarters through the provinces (Owino, 1997).

GoK health services are organised through a network of facilities organised in a pyramid, starting from dispensaries to sub-health centres and health centres at the bottom through to rural health training centres, sub-district hospitals, district hospitals, provincial general hospitals and at the apex, the Kenyatta National Hospital (KNH) (Figure 2.4). Facilities become increasingly complex in diagnostic, therapeutic and rehabilitative services at the upper levels, which serve as the referral levels (Owino, 1997; Noor *et al.*, 2004). Out-patient and in-patient services are provided largely by hospitals and some health centres (Noor *et al.*, 2004). In addition to these facilities, a number of specialist facilities at both district, provincial and national levels provide additional support. For instance, Mathare Mental Hospital serves as a national referral centre for mental illnesses. Other facilities include maternity hospitals and those for diseases like tuberculosis or conditions that require specialist treatment, for instance spinal injuries (Noor *et al.*, 2004).

At the district level, facilities are managed by a District Health Management Team (DHMT), which implements the decisions of the DHMB. Although GoK health facilities are categorised as described above, in reality, there are difficulties distinguishing between middle levels of service, i.e. dispensaries versus clinics, sub-health centres versus health centres, and rural health training centres versus sub-district hospitals. This is because decisions made by the DHMTs to provide staffing are based upon actual patient load rather than infrastructure criteria on which the classification is based (Noor *et al.*, 2004).

There are no systematic audit structures or processes that measure the quality of care at GoK facilities; consequently, there are varying estimates of even the most basic of

indicators, i.e. the number of health facilities in Kenya (Owino, 1997; MoH, 2000; 2004a; Noor *et al.*, 2004). The most rigorously derived estimates come from the work of Noor and colleagues (2004, Table 2.1), which showed that there were 6,674 health facilities in Kenya in 2004 and approximately a third of these were run by the government. A further 18.2% were run by the mission and NGO sector and 1.4% by local authorities. Private sector facilities account for 44.2% of facilities mapped, a far greater estimate than previously thought, but still underestimated (Noor *et al.*, 2004).

Table 2.1: Breakdown of the 6,674 health facilities identified in Kenya in 2004 by type and service provider (Noor *et al.* 2004).

	MoH	**Mission/NGO**	**Ministry of Local Government**	**Employers and other ministries**	**Private sector**	**Total**
Hospitals*	125	96		11	107	339
Health centres†	473	157	50	24	26	730
Dispensaries	1,471	907	40	252	289	2,958
Unspecified clinics‡				45	2179	2,225
Specialist facilities§	8	54	5	5	350	422
Total	2,077 (31.1%)	1,214 (18.2%)	95 (1.4%)	337 (5.1%)	2,951 (44.2%)	6,674

* Includes provincial, district, sub-district hospitals or unspecified private hospitals offering general in-patient clinical services.
† Includes all health centres, sub-health centres and rural health training centres as specified on national databases.
‡ Includes all clinics that were not classified in the private or employer sectors that provide generalized health services but were not classed as dispensaries or health centres.
§ Includes all hospitals that provide treatment for only special diseases such as leprosy, tuberculosis, cancer, ophthalmology, spinal injury etc and the large number of maternity and nursing homes.

Figure 2.3: Organogram showing the organisation of the Ministry of Health (MoH), Kenya as defined in 2001.

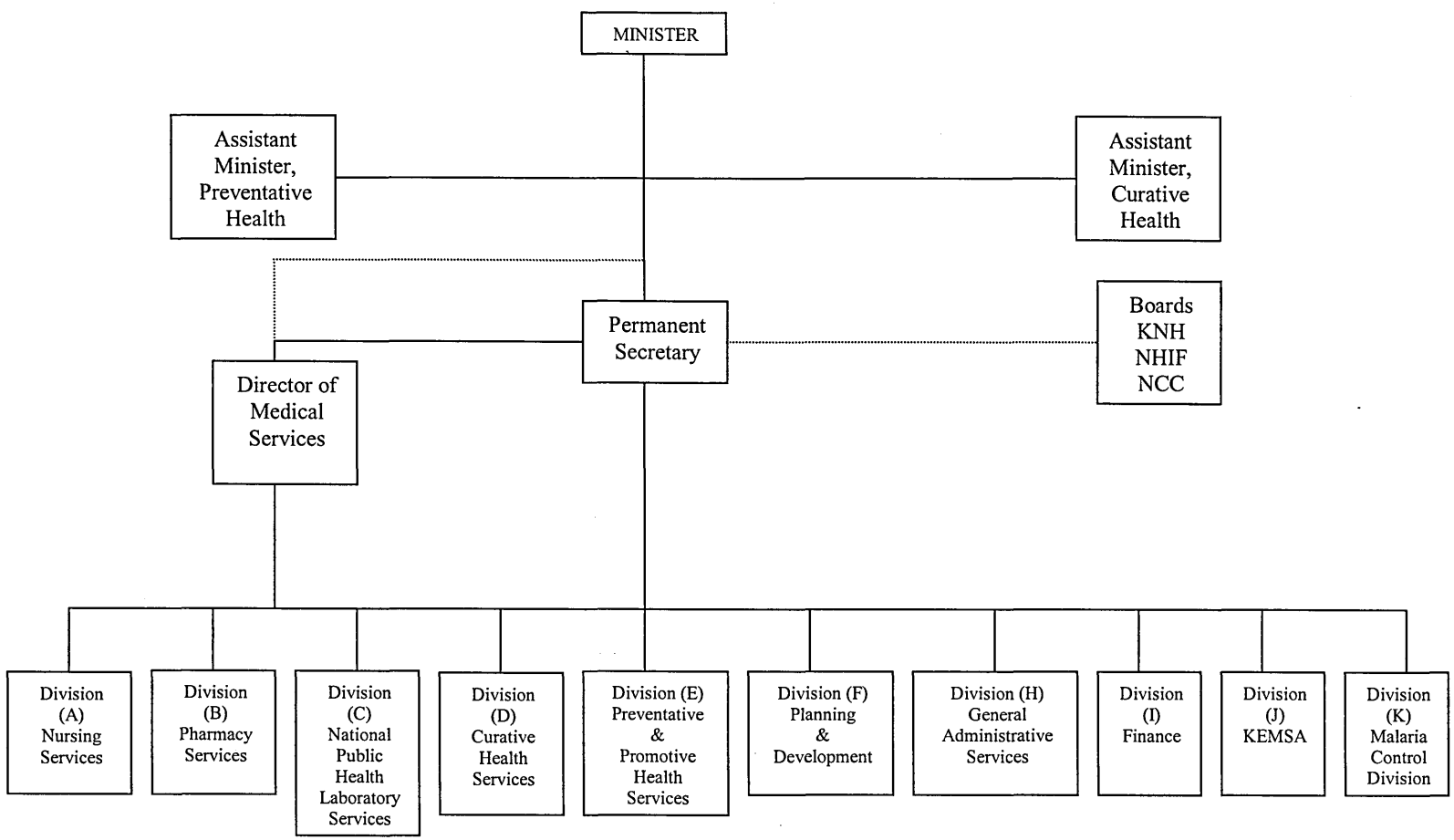
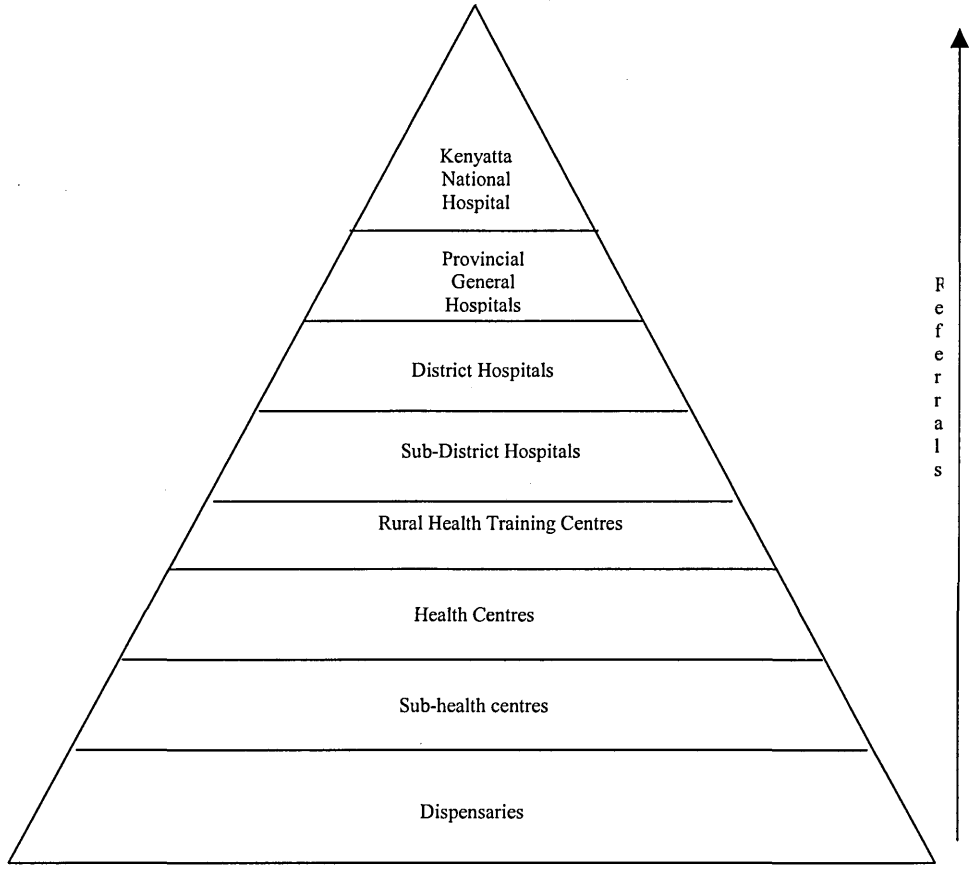


Figure 2.4: Pyramidal structure of the Government of Kenya (GoK) health services and referral system.



2.2.3 Health sector reform and health financing

From independence, the Kenya government placed a high premium on the health of its citizens. Plans were put in place to ensure equitable distribution of income, access to education and health services and a long-term objective to provide free basic health services to all citizens. In 1965, the government introduced free outpatient medical services throughout the country (Schwartz, 1996). Free healthcare, however, proved untenable as the number of health facilities expanded countrywide leading to a major strain on the government budget. For instance, total GoK spending on health increased from KES 255.4 million (USD 36.0 million) in 1972 to KES 1.3 billion (USD 234.0 million) in 1996[5]. This was compounded by structural adjustment programmes in the 1980s introduced by

[5] The Central Bank of Kenya mean exchange rate of the Kenya Shilling (KES) to the US dollar in 1972 was 7.14 and 56.96 in 1996 (Mr. A Haret, personal communication).

development partners whose main requirement was a cut-back on government expenditure, resulting among other things, in decreased spending on health care and consequent decline in quality of services provided (Owino, 1997).

The moves toward free universal health care for all Kenyans that were taken immediately following independence were gradually replaced in the 1980s and 1990s with user charges and cost sharing (Owino, 1997), and Kenya seems to have come full circle by 2004 when high level discussions were initiated on ways to introduce free health care for all. A Sessional Paper (Sessional Paper No. 2 of 2004) and a bill (The National Social Health Insurance Fund Bill, 2004), which seek to reintroduce free health care in Kenya, were published by the government (GoK, 2004; MoH, 2004a) on May 28th 2004. The bill was subsequently tabled, discussed, and passed by parliament in December 2004, but is yet to receive presidential assent to make it law (http://www.nationmedia.com, accessed 14/12/04).

2.3 Malaria in Kenya

Kenya has a diverse ecology that supports the entire range of stable and unstable *P. falciparum* transmission conditions (Snow *et al.*, 1998) and malaria is a major public health risk in the country. The MoH's Health Management Information Systems (HMIS) has collected imperfect data over the years by way of monthly reports from GoK facilities countrywide. Between 1996 and 1999, only 34 to 40% of facilities made submissions to headquarters, however, malaria was consistently reported as the leading cause of morbidity in Kenya accounting for approximately 30 to 34% of outpatient attendances over this period (representing over 4 million new cases of malaria annually) (HMIS, 2001).

Although malaria affects millions of Kenyans per year, pregnant women and children below the age of five years are most at risk. Snow *et al.* (1998) have modelled the risks of malaria morbidity and mortality in Kenya using data from a variety of sources. In their study, the authors used data from 124 community-based, cross-sectional malaria parasite surveys conducted between 1966 and 1996 across Kenya among children aged 0 and 10 years and linked these with climate data for the country to define malaria endemicities using a climate suitability model. Data were further linked with the 1989 population census figures for Kenya and paediatric admission and demographic surveillance data from across Africa to derive risk estimates for malaria morbidity and mortality. Results indicated that in 1997, approximately eight million people were exposed to unstable malaria and five million were exposed to a low risk of stable transmission in Kenya. About four million people including 677,000 children were judged to live under areas of high transmission intensity, while over 11 million people were estimated to be exposed to intermediate levels of *P. falciparum* intensity. The authors concluded that in 1997 in Kenya, approximately 26,000 malaria deaths might have occurred among children aged less than five years and that approximately 145,000 children aged 0-4 years would require intensive clinical management for severe malaria in hospital. The figures increase with epidemics in epidemic-prone and low risk arid areas of Kenya (Table 2.2).

Table 2.2: Populations exposed to risk of different malaria endemicities in Kenya and risk estimates for mortality and morbidity (Snow *et al.*, 1998).

Feature	Rainfall Limiting Unstable malaria	Non-rainfall Unstable Malaria	Low Stable Endemicity (PR* < 20%)	Moderate Stable Endemicity (PR 20-69%)	High Stable Endemicity (PR >= 70%)
Number of locations	85	287	234	382	92
1997 projected total population	680,247	7,834,477	4,945,381	11,113,368	3,737,639
1997 projected 0-4 population	115,961	1,375,255	848,946	1,960,626	677,006
Malaria mortality estimates per 1000 children 0-4 years per annum (p.a.)	0 or in epidemic 29-125	0.55	0.55	9.33	9.77
Numbers of deaths 0-4 years each year	0 or 3,363 – 14,495	756	467	18,293	6,614
Malaria admission rates per 1000 children 0-4 years p.a. under different endemicities	-	21.38	21.38	38.58	32.30
Expected malaria admissions 0-4 years p.a.	-	29,403	18,150	75,641	21,867

* Parasite ratio

2.4 The Division of Malaria Control (DOMC) and the Kenya National Malaria Strategy (KNMS)

2.4.1 The DOMC

Until recently, malaria control activities in Kenya were largely subsumed under the activities of the Division of Vector Borne Diseases (DVBD). In the 1960s and 1970s for instance, this division was responsible for large-scale spraying of houses in western Kenya (Kisumu and Kericho) under both experimental and field conditions (Githeko, 1992) and as recently as 1998, the Malaria Control Unit (MCU) was operating from an office at DVBD (Snow *et al.*, 2001b). However, in October 2000, following restructuring of the MoH and pressure from bilateral donors on the need to raise the profile of malaria in Kenya, the MCU was upgraded to a full division within the MoH under the Department of Preventive and Promotive Health Services. A National Malaria Coordinating Committee was established to coordinate and make decisions on overarching strategic and managerial

issues. This committee, chaired by the PS MoH, is aided in its day-to-day activities by the DOMC which is the operational arm of the National Malaria Control Programme (NMCP) (Snow *et al.*, 2001b).

2.4.2 Development of the KNMS

In recognition of the public health importance of malaria in Kenya (Section 2.3), a need was identified for a concerted effort to control the disease. It was recognised that previous efforts to control the disease were piecemeal, sporadic and largely ineffective (MoH, 1998). Therefore, a series of consultative meetings involving over 200 stakeholders drawn from government and the private sector, Missions and non-governmental organisations (NGO's) at central, provincial and district level were held for consensus building on a number of issues pertinent to malaria control in Kenya. These series of meetings culminated in the adoption of a Kenya National Malaria Strategy (KNMS) launched in April 2001 whose main objective is "...to reduce the level of malaria infection and consequent death in Kenya by 30% by the year 2006, and to sustain that improved level of control to 2010".

The KNMS is in line with the broader Health Sector Strategic Plan where malaria is seen as part of six essential health packages to be delivered to Kenyans in a co-ordinated manner at the national, provincial, district and community levels by all stakeholders in the health sector. These six essential health packages are reproductive health, immunisation (Kenya Enhanced Programme on Immunisation, KEPI), Integrated Management of Childhood Illness (IMCI), control of HIV/AIDS, malaria, and that of environmentally related communicable diseases such as cholera, typhoid, and dysentery. The KNMS has four main pillars of disease management and prevention which are envisaged will help

achieve its aims and objectives (DOMC, 2001a). The four pillars are congruent with those of the RBM initiative (Section 1.5.2.1) and comprise the following:

1. Effective case management of malaria at all levels of the health care system
2. Prevention of malaria in pregnancy
3. Increased and equitable access to insecticide treated bed nets (ITN) by at-risk groups (pregnant women and children under five years of age)
4. Early detection and containment of epidemics

These four pillars are supported by two crosscutting strategies: Information, Education, and Communication (IEC) to arm the public with preventative and treatment knowledge; and Monitoring, Evaluation and research to update and inform malaria control strategies (DOMC, 2001a).

2.4.3 Role of DOMC in antimalarial drug use and quality

The role of the DOMC in drug use and quality is to ensure the rational use of efficacious, safe, quality antimalarial drugs in the case management of malaria and to ensure the constant supply of essential malaria drugs to communities in Kenya. To this end, the KNMS states that the DOMC will "... set policy and guidelines to ensure that:

1. All fevers are treated as early as possible and as close to a patient's home as possible, with acceptable quality and correct dosages of the first line antimalarial drugs and supportive treatment.
2. First line therapeutic failures will be appropriately referred and managed with recommended second line treatment, and
3. All complications of malaria will be referred and managed according to national guidelines..."

The responsibility of overseeing that drugs are safe, efficacious, and of acceptable quality at registration and post-registration has been invested in the existing government

structures, i.e. the Pharmacy and Poisons Board (PPB) of the MoH (of which the National Quality Control Laboratory (NQCL) is an arm). Ensuring constant supply of essential malaria drugs has likewise been invested in the existing Kenya Medical Supplies Agency (KEMSA). The structure and functions of these bodies are covered in more detail in Chapter 3.

In addition to allocating responsibility for the various components of the KNMS to the appropriate stakeholders, the KNMS also set targets for key strategies to be met and a clear monitoring and evaluation strategy to evaluate progress towards these targets. The following represent mid-term targets set for 2006 for drug use, quality and attendant IEC needs (DOMC, 2001a):

1. 80% of households at risk will receive targeted IEC materials
2. 80% of GoK facilities will have continuous and adequate supplies of drugs essential for the management of malaria
3. 80% of all antimalarial drugs provided through the public and private sectors will be of internationally acceptable standard of quality
4. 60% of all fevers which are treated at home by family members or caretakers will be managed appropriately
5. 80% of all cases of fever treated by community health workers (CHWs) or outpatient facilities will be managed according to national recommendations
6. 80% of first line therapeutic failures and severe, complicated malaria cases will be correctly managed by health personnel in appropriate health facilities.

A clear and consistent message throughout the KNMS is the importance of co-opting health workers and communities in achieving its goals. Clear guidelines have been developed for appropriate case management of malaria by health workers, the most notable being the National guidelines for diagnosis, treatment and prevention of malaria for health workers (DOMC, 1998). IEC materials have also been developed to pass important

messages to communities. The most notable are DOMC charts and posters for correct doses of first-line drugs and quality-assured brands of first-line drugs (see Chapter 5 for the coverage of these materials). More recently, a number of commercials have appeared in the print and electronic media on the need to treat malaria promptly with the right drugs and to protect pregnant women and children under five with ITN (http://www.nationmedia.com, accessed 07/12/04).

2.5 Treatment seeking for fevers and malaria in Kenya

Broad issues related to patterns of treatment seeking behaviour have been presented in Section 1.8; in this Section, the Kenya context is specifically reviewed. A number of studies have been carried out in Kenya on treatment seeking for fevers and malaria. From these studies, key themes have emerged which can be summarised as follows: first, Kenyan communities plagued by malaria and fevers have elaborate combined bio-medical and bio-cultural vernacular to describe fever and malaria. Significantly, local concepts of malaria overlap in many ways with clinical definitions of malaria although there are conditions that are locally called "malaria", which are not always malaria (Mwenesi *et al.*, 1995; Munguti, 1998; Baume, 2002).

A second important observation from studies of treatment seeking for fever and malaria in Kenya is that most fevers are treated outside the formal health sector, mostly with shop-bought antipyretic or antimalarial drugs administered at home. Figures 2.5 to 2.7 summarise the proportion of fevers first treated at various sources across a number of sites in Kenya. Only a minority of studies indicate greater than 50% use of the formal sector (Mwabu, 1986; NCPD, 1989; 1994; 1999; Munguti, 1998; CRS, 1999; Garg *et al.*, 2001; Kaburu, 2002; CBS, 2003) with most studies showing borderline use of the formal sector or greater use of the retail sector (Ongore *et al.*, 1989; Boerma, 1990; Snow *et al.*, 1992;

UNICEF & CBS, 1992; Mwenesi *et al.*, 1995; Ruebush *et al.*, 1995; Molyneux *et al.*, 1999; PCA, 2000; Hamel *et al.*, 2001; Baume, 2002; Nyamongo, 2002). Distance, costs and unavailability of drugs in most public facilities, are often cited as the reasons why the retail sector plays an important role in the treatment process often forming the first choice in seeking treatment (Nantulya *et al.*, 2001). Between 0 and 25% of fevers remain untreated or are managed using prayers (Mwabu, 1986; Boerma, 1990; UNICEF & CBS, 1992; Mwenesi *et al.*, 1995; Ruebush *et al.*, 1995; Munguti, 1998; Molyneux *et al.*, 1999; Hamel *et al.*, 2001; Kaburu, 2002; Nyamongo, 2002).

Third, treatment seeking for fevers and malaria in Kenya is usually described as a hierarchical process where caretakers or patients first seek easily available or cheaper alternatives before progressing to the formal sector in the course of the illness. The use of multiple sources of treatment for the same fever episode is, therefore, common with the typical patient first self-medicating with shop-bought anti-malarial and antipyretic drugs before presenting to the health facility (Snow *et al.*, 1992; Nyamongo, 1998; 1999; 2002; Marsh *et al.*, 1999; Kaburu, 2002).

Figure 2.5: Percentage of fevers first treated at formal public and/or private facilities in Kenya.

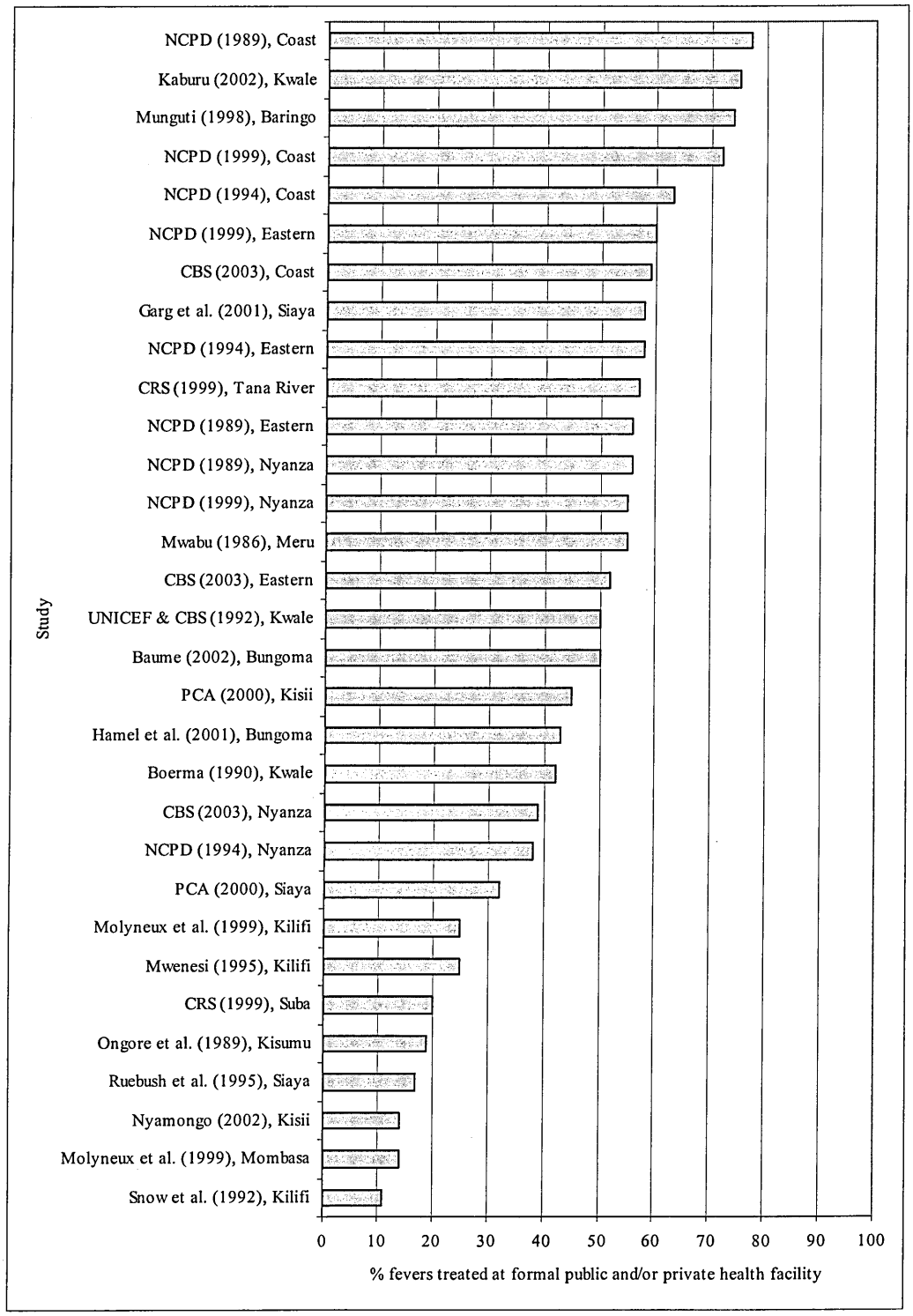


Figure 2.6: Percent of fevers first treated using drugs at home or obtained from shops, pharmacies, and mobile vendors in Kenya.

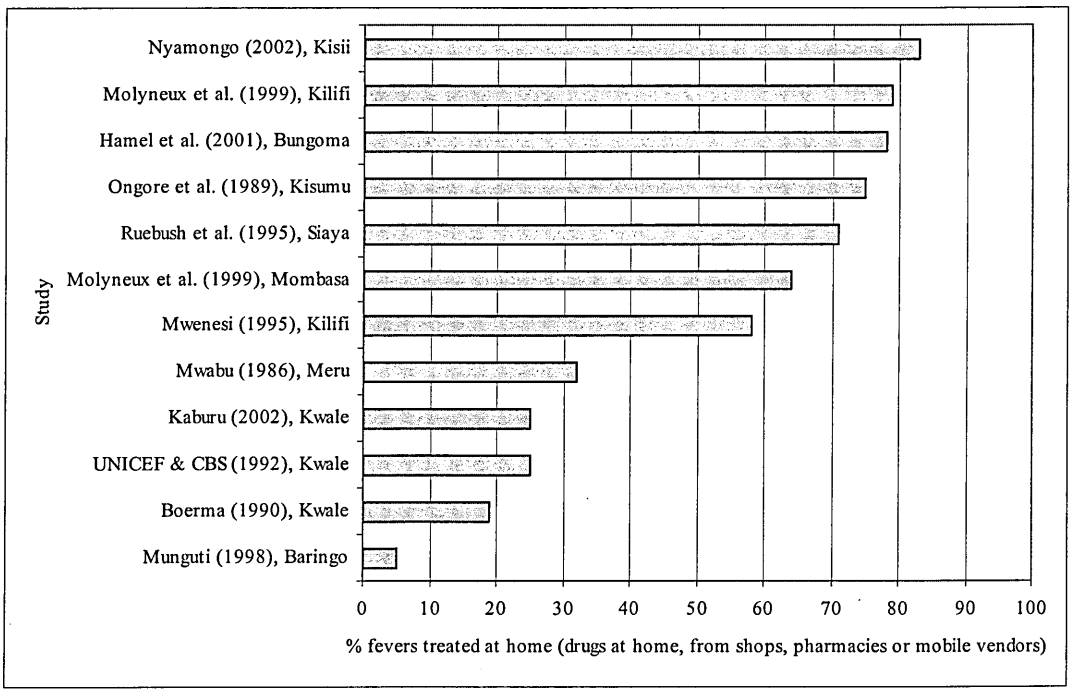
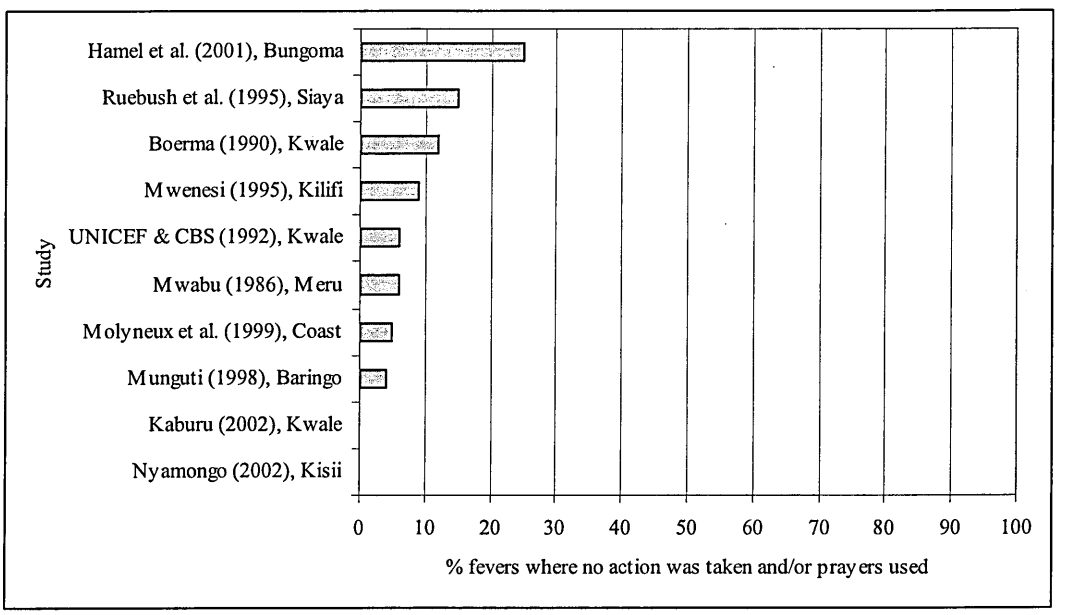


Figure 2.7: Percent fevers where no action was taken or where prayers were used in Kenya.



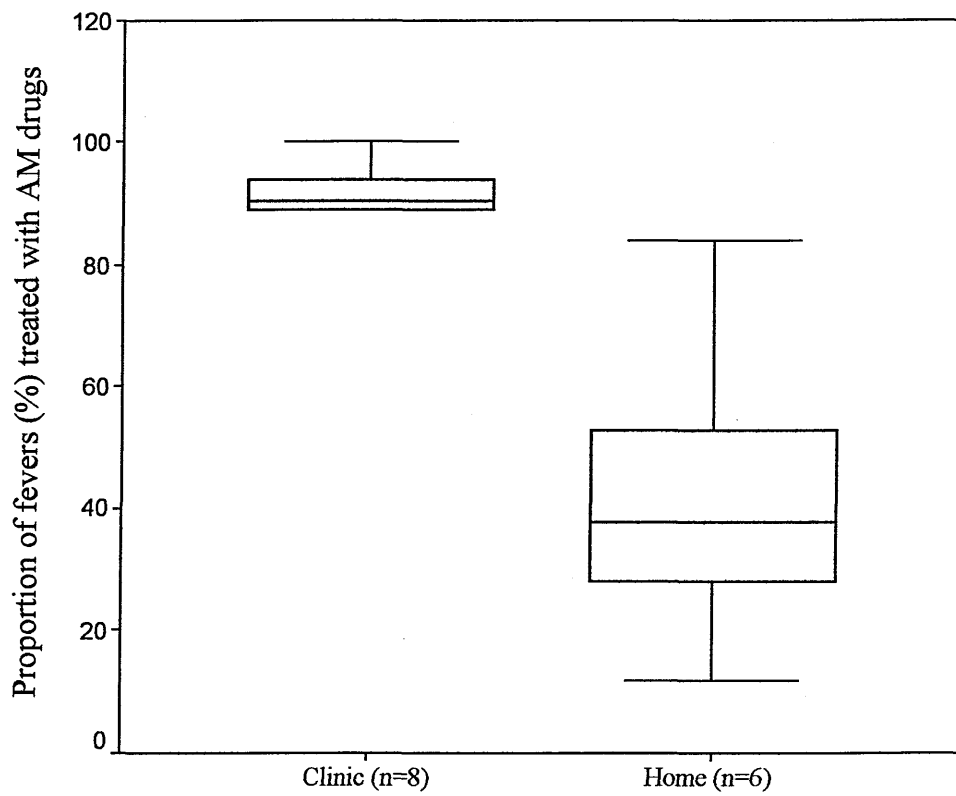
Further, a waiting period (usually one to three days) before seeking treatment when the severity of the fever or illness is monitored is not uncommon (Mwenesi *et al.*, 1995; Ruebush *et al.*, 1995). Among children, adult involvement is crucial in treatment seeking. In a study among primary schoolchildren aged 11 to 17 years (median age 13 years) in Bondo district, 81% of illness episodes without adult involvement remained untreated, while 19% were treated by the children themselves. Older children were more likely to self-medicate than younger ones; boys were also more likely to self-medicate than girls (Geissler *et al.*, 2000).

2.5.1 Use of antimalarial drugs

Most fevers in Kenya are treated with western pharmaceuticals and only a small proportion is treated with non-western interventions. Of fevers treated with western pharmaceuticals, the most widely used class of drugs are the antipyretic drugs, followed by the antimalarial drugs (Snow *et al.*, 1992; Mwenesi, 1994; Mwenesi *et al.*, 1995; Molyneux *et al.*, 1999). There are varying estimates as to the proportion of fevers treated with antimalarial drugs in Kenya and this depends on the source of treatment. Figure 2.8 is derived from 11 studies carried out in eight districts in Kenya between 1980 and 2002, and shows proportion of fevers treated with antimalarial drugs from formal clinics and at home. The studies demonstrate that a little over a third of fevers [Median 38%, Interquartile range (IQR) 28% to 53%] managed at home are treated with antimalarial drugs (Schulpen & Swinkles, 1980; Snow *et al.*, 1992; Mwenesi *et al.*, 1995; Ruebush *et al.*, 1995; Hamel *et al.*, 2001; Kaburu, 2002). Conversely, 91% (IQR 89 to 94%) of fevers treated at formal clinics receive an antimalarial drug (Mwenesi *et al.*, 1995; Ruebush *et al.*, 1995; Abuya, 2001; Zurovac *et al.*, 2004).

Fevers treated at home are usually managed with shop-bought antipyretic and antimalarial drugs (Marsh *et al.*, 1999; Molyneux *et al.*, 1999); therefore, the types of antimalarial drugs used to manage such fevers vary with time and place and depend on what is commonly stocked in the local shops and pharmacies. Conversely, the types of antimalarial drugs obtained from the formal sector tend to be more uniform since drug supply to this sector is by a few select suppliers who have won the national tender. Nonetheless, patients are usually unable to identify the brand names of antimalarial drugs dispensed to them from the public sector (including the mission sector) because tablets are typically dispensed from large multi-dose containers into small envelopes while suspensions are dispensed in bottles (from large multi-dose containers) brought by patients (Zurovac *et al.*, 2003).

Figure 2.8: Use of antimalarial drugs among recent fevers in Kenya as described by 11 studies conducted between 1980 and 2002 in eight districts of Kenya.



2.5.2 Adherence to antimalarial dosage regimen

Despite the importance of adherence to the antimalarial drugs for effective case-management, not many studies have been done in this area in Kenya. In one study in Bungoma district, among 79 recently febrile children given chloroquine (CQ) at home, 62% received less than 20mg/kg of the drug (recommended dosage 25mg/kg) (Hamel *et al.*, 2001). In another study in Kilifi district, Marsh and colleagues (1999) reported that only 2.8% of children who had received CQ had been given an adequate dose of 25mg/kg for the recommended three-day period (adequate adherence). In yet another study on CQ use among school children in Siaya district, only in 12% of cases was the correct dose of CQ administered and in the rest the dose was inadequate (Ruebush *et al.*, 1995). In Busia in 2003 among recently febrile children under five years of age, Marsh *et al.* (2003) found that 11% of those who purchased amodiaquine (AQ) from shops and 50% of those who had purchased sulfadoxine/pyrimethamine (SP) had received the right amount of drug for the right duration (Marsh, 2003). In short, the few studies that have addressed adherence to antimalarial drugs obtained from the retail sector in Kenya suggest that adherence to one-day antimalarial regimen is generally better than that to multiple regimen and that under-dosing is more common than over-dosing, especially among children.

Adherence in the public formal sector is at two levels: first, is whether health workers prescribe the first-line antimalarial drug to patients with clinical or confirmed malaria; second, is if health workers prescribe the nationally recommended dosages. Zurovac *et al.* (2005) carried out an audit of case management of malaria among children below the age of five in Greater Kisii, Kwale, Bondo and Makueni districts between July 2001 and February 2002. At the time of the surveys, SP was the recommended first-line treatment for uncomplicated malaria at a dose of 25mg/kg body weight for the sulfonamide component, which is usually in a fixed combination with pyrimethamine in a ratio of 20:1.

The authors report that only 55% of children presenting with fever to GoK outpatient departments were managed with SP and only in 34% of cases was an adequate dose consistent with national guidelines given. In a similar survey among older children (5-14 years) and adults (>14 years) in Greater Kisii and Kwale districts between August 2002 and May 2003, 67% of patients received SP and 84% of these patients received the nationally recommended dose (Zurovac *et al.*, 2003).

The WHO recommended dose of SP (calculated using 25mg/kg body weight of the sulfonamide component) is usually translated into age tables by the DOMC and children within a given age bracket are given the same dose of SP, e.g. children aged 3 to 11 months are given half a tablet of SP (one tablet contains 500mg sulfadoxine or sulfalene and 25mg of pyrimethamine). Terlouw *et al.* (2003) argue that use of these tables has led to underdosing in the past and consequent decline in SP efficacy. Based on body weight, they estimate that 73% of children aged <24 months received less than the target dose and that underdosing accounted for 26% of cumulative treatment failures among these children. However, after the guidelines were revised in 1998 (doses increased for certain age groups), only 4.2% of patients received less than the recommended dose and consequently there was no association between dosing practices and treatment failure.

2.6 Antimalarial drug resistance and drug policy in Kenya

In this section, issues relating to drug policy, its formulation, and implementation are discussed in detail because case management of clinical cases of malaria, which is the cornerstone of the KNMS can only take place within a favourable policy framework. Antimalarial drug resistance continues to pose a threat to this strategy. Kenya changed first-line antimalarial policy from CQ, which had been the mainstay of treatment for 50 years since its introduction in the 1930s, to "sulphur"-pyrimethamine (SP) combinations in 1998. In 2004, the policy was changed again to artemether-lumefantrine (ART-LUM) as first-line therapy following the precipitous decline in the clinical efficacy of SP. The efficacy of SP and amodiaquine (AQ), which have remained the most popular first and second-line therapies for malaria until recently, are reviewed. The attendant issues in antimalarial drug policy changes, especially the implications for artemisinin-based combination therapies (ACT) such as ART-LUM and the role of the East African Network for Monitoring Antimalarial Treatment (EANMAT), a regional network for monitoring *P. falciparum* resistance to antimalarial drugs are discussed.

2.6.1 Efficacy of antimalarial drugs in Kenya and the East African Network for Monitoring Antimalarial Treatment (EANMAT) countries

Drug policy changes in Kenya, like elsewhere in the sub-region, are based on an efficacy model where changes are envisaged as occurring in phases (see Section 1.7.5). Clinical efficacy data in the sub-region are generated largely under the auspices of EANMAT. EANMAT was formed in 1998 to monitor the clinical resistance of *P. falciparum* to nationally recommended first and second-line antimalarial drugs. EANMAT is a collaborative venture between the National Malaria Control Programmes within the ministries of health of the five member states of Kenya, Uganda, Tanzania (mainland Tanganyika and the island of Zanzibar), Rwanda and Burundi and is managed by a

secretariat that meets every three months to share data, technical difficulties and policy implications. In addition to the secretariat, each country has a national team responsible for the co-ordination of all EANMAT in-country activities. EANMAT has sentinel districts in each member country (EANMAT, 2001).

In Kenya, there are eight EANMAT sentinel districts for prospective surveillance of efficacy of antimalarial drugs using lot quality assurance sampling[6] and standardised WHO *in vivo* efficacy testing protocols (see Section 1.7.3 for measurement of antimalarial drug resistance). The sentinel districts were chosen to be representative of the local range of ecological and epidemiological conditions (EANMAT, 2001; 2003). Where possible, tests are conducted among children under five years of age (6-59 months) suffering from uncomplicated *falciparum* malaria recruited in the sentinel sites in each member country using standard inclusion criteria (Table 2.3).

Table 2.3: Inclusion criteria for recruiting children into EANMAT clinical efficacy studies at sentinel sites (EANMAT, 1999).

Criteria
• Age between 6 and 59 months
• No general danger signs or severe malaria present
• No other cause of fever is detectable
• No severe malnutrition
• Patient has only *P. falciparum* with parasite counts between 2000-100,000/µl of blood
• Patient has understood the procedures of the study and has agreed to participate
• Patient is able to come for stipulated follow up visits and has easy access to the health unit
• History of fever within 24 hours or axillary temperature >= 37.5°C but < 39.5°C at the visit
• For those on SP: patient has no history of skin rashes after sulphonamide use and patient has no skin conditions such as eczema that might be mistaken for reactions to sulphonamides

The unique placement of EANMAT within ministries of health affords a sense of data ownership and consequently an effective mechanism to provide direct operational

[6] Lot quality assurance sampling (LQAS) is a technique that was developed in the pharmaceutical industry to help in decisions as to what products to release into the market. Using statistical means, a predetermined number of samples are set as "acceptable failures" for every batch or lot of a given product intended for the market. Any failure rates more than this level means the entire batch or lot will be rejected. The technique has been adopted in health research and interventions in developing countries. For instance, intervention studies for HIV/AIDS typically set a certain level of awareness in the community as acceptable. Anything below that is deemed inappropriate and therefore intervention programmes are instituted to raise the level of awareness (Lanata & Black, 1991).

monitoring and evaluation data to support policy (EANMAT, 2001; 2003; MoH, 2001a). A key unresolved question in first-line drug policy changes in Kenya is what proportion of EANMAT sentinel sites need to report clinical failure rates above 25% to warrant change in policy. This has been, and continues to be, the subject of debate (EANMAT, 2003).

2.6.2 Drug policy changes and the efficacy of antimalarial drugs in Kenya

The evidence that led to the 1998 policy change from CQ to SP and the attendant political issues have been reviewed by Shretta *et al.* (2000). In summary, 49 studies on CQ among populations less than 18 years of age throughout the country with different definitions of favourable outcome (see footnotes) were abstracted and analysed. Between 1979 and 1990, 34% of all studies had demonstrated that 25% of recruited children were unable to clear infections by day 7[7]. Six of 10 (60%) studies showed that 25% of the study populations were unable to clear infections by day 14[8] and 5/17 (29%) studies reported >14% of subjects with RIII[9] resistant infections. Between April 1987 and October 1997, eight studies, which employed the revised, WHO definitions of clinical failure[10] were undertaken and seven indicated unacceptable levels of CQ failure (i.e. clinical failure rates >=25%).

Despite mounting evidence, the Kenyan MoH was reluctant to change policy from CQ to SP, which was considered more efficacious, and the only practicable, affordable alternative promoted by WHO and listed on the Kenya Essential Drugs List (AQ was not on the list at the time due to concerns about its safety). This reluctance to effect policy change was attributed to a general lack of consensus on the principles for assessing drug failures, the

[7] WHO standard *in vivo* 7-day test. Test based on parasitological outcome and policy change suggested when parasitological failure rates >=25% on day 7 (Schapira *et al.*, 1993b).
[8] WHO extended 14 day *in vivo* test. Test based on parasitological outcome and policy change suggested when parasitological failure rates >=25% on day 14 (Schapira *et al.*, 1993b).
[9] RIII resistance is defined as clearance of asexual parasites by less than 75% during the first 48 hours of treatment. >14% RIII resistance deemed unacceptable by the authors (Sudre *et al.*, 1992).
[10] Adequate Clinical Response (ACR) on day 14 i.e. absence of fever or parasitaemia (WHO, 1996).

inclusion criteria for the study subjects and the relative benefits of parasitological over clinical assessments. After much debate, a decision was finally taken to change first-line antimalarial policy from CQ and revised treatment guidelines launched, approving the use of SP in August 1998 (Shretta *et al.*, 2000).

Between 1998 and 2004, the first-line antimalarial drug recommended for use in Kenya was SP with AQ and oral quinine (QN) reserved as second-line treatment (DOMC, 1998). Tables 2.4 and 2.5 show a summary of contemporary EANMAT (http://www.eanmat.org, accessed 28/08/04) and non-EANMAT (Obonyo *et al.*, 2003; Alloueche *et al.*, 2004; Makanga *et al.*, personal communication) clinical efficacy data for SP and AQ in Kenya between the years 1999 to 2003. Using the new WHO definition of adequate clinical and parasitological response (ACPR) on day 14 (see Section 1.7.3), the data suggest that SP clinical failure rates were well above the 25% cut-off for most studies. In 1999, none of the three EANMAT studies showed ACPR below 75% (or clinical failure rates above 25%). By 2000 and 2001 however, the share of studies showing ACPR below 75% had risen to 58% and 50%, respectively, further increasing to 75% in 2003.

With increasing resistance to SP (EANMAT, 2001; 2003), Kenya was faced with no option but to change first line therapy once again. The options were: 1) moving AQ from second-line treatment to first-line therapy; 2) combining SP with artesunate (SP-AS) or AQ with artesunate (AQ-AS); 3) or using ART-LUM. Because of the WHO's position on ACT, AQ monotherapy was not an option. SP was failing; therefore, combining a failing drug with an efficacious one (AS) did not make for a rational therapeutic choice. Likewise, AQ-AS was opposed since *P. falciparum's* sensitivity to AQ was also showing evidence of decline by day 28 and widespread use of AQ as monotherapy in the retail sector precluded its

combination with other drugs as a long-term solution. First-line policy was therefore changed to the only remaining option, ART-LUM (DOMC, 2004a).

Because of the cost implications and the fact that the use of ART-LUM under operational conditions has not been investigated, it has been proposed that the new first-line policy in Kenya be introduced in a staggered manner over a five-year period. It has been proposed that in the first two years (2004-2005), free doses of ACT will be provided to all patients presenting to GoK and mission health facilities. In the third year (2006), private service providers will be incorporated. In the fourth and fifth years (2007-2008), after safety of ART-LUM under operational conditions has been ascertained, mechanisms will be put in place to widen access to ART-LUM by including it in the general sales list to enable its sale over the counter (OTC) in the retail sector. Because of the staggered nature of the policy change, AQ will be promoted as the best alternative to SP among private service providers, including the retail sector, until ART-LUM can be availed in these sectors (DOMC, 2004b).

Table 2.4: Day 14 clinical efficacy outcomes of SP studies conducted in various sites in Kenya between 1999 and 2003.

Site	Date	Source	Completed follow-up	% ETF* + LTF*	% ACR*	% LPF*	% ACPR*
Busia	1999	EANMAT	44	6.8	93.2	2.3	90.9
Kisumu	1999	EANMAT	36	11.1	88.9	0.0	88.9
Kirinyaga	1999	EANMAT	39	17.9	82.1	0.0	82.1
Bondo	2000	EANMAT	60	26.7	73.3	6.7	66.7
Kibwezi	2000	EANMAT	11	18.2	81.8	0.0	81.8
Kirinyaga	2000	EANMAT	59	18.7	81.3	20.3	61.0
Kisumu	2000	EANMAT	65	38.5	61.5	6.1	55.4
Busia	2000	EANMAT	57	7.0	93.0	19.3	73.7
Lamu	2000	EANMAT	45	0.0	100.0	2.2	97.8
Kwale	2000	EANMAT	63	0.0	100.0	3.2	96.8
Bungoma	2000	AMREF	48	35.4	64.6	0.0	64.6
Sirisia	2000	AMREF	44	27.3	72.7	0.0	72.7
Webuye	2000	AMREF	46	19.6	80.4	0.0	80.4
Kilifi	2000	Alluoche *et al.* 2004	62	17.7	82.3	0.3	82.0
Siaya	2000	Obonyo *et al.* 2003	191	25.7	74.3	0.0	74.3
Kibwezi	2001	EANMAT	19	15.8	84.2	10.5	73.7
Kirinyaga	2001	EANMAT	33	36.3	63.7	15.2	48.5
Busia	2001	EANMAT	57	8.9	91.1	10.5	80.7
Kwale	2001	EANMAT	53	7.6	92.4	5.7	86.8
Nandi	2001	EANMAT	46	6.5	93.5	10.9	82.6
Mwea	2001	AMREF	28	21.4	78.6	0.0	78.6
Kibwezi	2002	EANMAT	31	51.6	48.4	3.2	45.2
Kisumu	2002	EANMAT	59	3.4	96.6	13.6	83.1
Bondo†	2003	EANMAT	112	21.4	78.6	16.1	62.5
Kibwezi‡	2003	EANMAT	71	8.5	91.6	8.5	83.1
Gucha§	2003	EANMAT	108	29.6	70.4	0.0	70.4
Kilifi	2003	Makanga *et al.* personal communication	641	32.8	67.2	0.0	67.2

* See Table 1.2 for efficacy definitions
† Day 28 ACPR of SP for this study was 30.9%.
‡ Day 28 ACPR for SP for this study was 46.4%.
§ Day 28 ACPR for SP for this study was 39.6%

Table 2.5: Day 14 clinical efficacy outcomes of AQ studies conducted in various sites in Kenya between 1999 and 2003.

Site	Date	Source	Completed follow-up	% ETF* + LTF*	% ACR*	% LPF*	% ACPR*
Bondo	1999	EANMAT	46	0.0	100.0	0.0	100.0
Kirinyaga	1999	EANMAT	25	16.0	84.0	4.0	80.0
Busia	1999	EANMAT	39	12.9	87.1	0.0	87.1
Bondo	2000	EANMAT	59	0.0	100.0	0.0	100.0
Kibwezi	2000	EANMAT	14	7.1	92.9	0.0	92.9
Kirinyaga	2000	EANMAT	61	1.7	98.3	6.6	91.8
Kisumu	2000	EANMAT	55	7.3	92.7	1.8	90.9
Kisumu	2000	EANMAT	26	23.2	76.8	0.0	76.9
Busia	2000	EANMAT	60	0.0	100.0	0.0	100.0
Lamu	2000	EANMAT	36	2.8	97.2	0.0	97.2
Kwale	2000	EANMAT	64	0.0	100.0	1.6	98.4
Bungoma	2000	AMREF	66	10.6	89.4	0.0	89.4
Sirisia	2000	AMREF	43	16.3	83.7	0.0	83.7
Webuye	2000	AMREF	50	4.0	96.0	0.0	96.0
Kibwezi	2001	EANMAT	25	16.0	84.0	0.0	84.0
Kirinyaga	2001	EANMAT	37	8.1	91.9	16.2	75.7
Busia	2001	EANMAT	61	3.3	96.7	3.3	93.4
Kwale	2001	EANMAT	57	0.0	100.0	0.0	100.0
Nandi	2001	EANMAT	51	2.0	98.0	0.0	98.0
Mwea	2001	AMREF	31	38.7	80.7	0.0	61.3
Kibwezi	2002	EANMAT	34	0.0	100.0	0.0	100.0
Kisumu	2002	EANMAT	54	0.0	100.0	1.9	98.1
Bondo†	2003	EANMAT	114	0.9	99.1	0.9	98.2
Kibwezi‡	2003	EANMAT	95	8.4	91.6	3.2	88.4
Gucha§	2003	EANMAT	131	5.3	94.7	0.0	94.7

* See Table 1.2 for efficacy definitions
† Day 28 ACPR of AQ for this study was 83.0%
‡ Day 28 ACPR of AQ for this study was 68.5%
§ Day 28 ACPR for AQ for this study was 77.0%

2.7 The political issues related to the new antimalarial drug policy

Antimalarial drug (AM) policy changes in Kenya are as much a political as they are a scientific exercise. As demonstrated by Shretta *et al.* (2000) in the case of the change from CQ to SP, overwhelming scientific evidence in support of policy change was not necessarily translated into speedy action. On the contrary, there was a long-drawn out consensus building process before a decision was finally taken to abandon CQ. In this section, Walt and Gilson's (1994) policy analysis model will be used to *describe* the political issues surrounding the new AM policy change. The model is used to *organise* the goings-on into context, content, processes, and actors, and is not an attempt at health policy analysis which would require a critical appraisal of the model itself and its usefulness vis-à-vis other competing constructs.

2.7.1 The context

The Kenyan economic and health sector context has already been discussed in the preceding sections. In addition, significant developments which have taken place in the Kenyan political landscape over the past few years are likely to have an impact on the new policy. The most important occurred in December 2002 when a new, progressive government was elected by an overwhelming majority of Kenyans after decades of rule by a *de facto* single party, authoritarian regime. The new coalition government was largely elected on an anticorruption platform, free primary education, free health care for Kenyans, and a promise to complete the constitutional review process, which had stalled under the previous regime.

Dissatisfaction in the ranks emerged soon after the elections, largely occasioned by the fact that part of the ruling coalition reneged on a pre-election pact that was meant to clip the excessive powers of the presidency (allegedly abused in the past) by creating the office of

an executive Prime Minister. This pact was to be delivered through a new constitutional dispensation, but the constitutional review process is still in limbo, much to the chagrin of those who are unhappy with the *status quo*. In this hostile political environment, leaks of scandals in the corridors of power were not uncommon. Chief among these was the single sourcing of passports from the UK-based Anglo-Leasing Limited (dubbed "Anglo-Fleecing" by the media) (http://nationmedia.com, accessed 07/12/04), contrary to GoK procurement rules, which stipulate competitive bidding for most government contracts. This saw the exit of a number of Permanent Secretaries from government and a cabinet reshuffle, resulting significantly in a new PS in the MoH in the midst of the policy change process described below. A wary Ministry of Finance (MoF), new faces at the MoH, dwindling donor confidence, and score settling within the government made for a challenging political context for ART-LUM.

2.7.2 The process

A number of consensus building workshops and meetings were organised by the DOMC from November 2003, under the auspices of the Drug Policy Technical Working Group (DPTWG) and its specialised sub-committees (drawn from a wide cross-section of national and international stakeholders) to iron out concerns of stakeholders and to come up with workable solutions. In this section, a description of this process is detailed.

In the first DPTWG meeting, preliminary evidence showing increasing SP failure was shared with the members and possible ACT replacements to failing SP monotherapy discussed. The need to test ACTs alongside SP and AQ monotherapies, the number of sentinel sites, avoidance of duplication of efficacy testing among the research community and adoption of the new WHO definition of day 28 ACPR, were agreed (DOMC, 2003a). In the second meeting, the deliberations revolved around the need for high quality data to

advocate for policy change, although some stakeholders were of the view that Kenya should not wait too long and should instead learn from the experiences of other African countries. It was noted Zambia and Zanzibar for instance had used baseline data on failure of existing therapies to change policy to ACT and did not wait until conclusive evidence on comparative efficacy of ACT was generated. Significantly and prophetically, the WHO delegation to the meeting reminded participants that the operational complexities of carrying out drug policy change needed to be tackled early on so as not to hinder the process (e.g. at what level ACT could be dispensed). In this meeting also, the DPTWG was requested to consider forming sub-groups to address the drug and non-drug issues arising from the imminent policy change (DOMC, 2003b).

In the third meeting, queries were raised on the quality of data that were being fronted in support of the proposed policy change with different stakeholders who had done studies on AQ and SP coming to different conclusions. For instance, EANMAT data suggested that AQ was still efficacious by day 14, yet the African Medical Research Foundation (AMREF) results showed a decrease in AQ efficacy. It was argued that differences could possibly be attributed to non-quality controlled drugs used among study subjects; members therefore urged the National Quality Control Laboratory (NQCL) to address drug quality issues more proactively. Members agreed to use similar definitions of treatment outcomes for data comparability and agreed to monitor efficacy of SP, ART-LUM, and AQ-AS in three sites in different ecological zones and harmonise the work of researchers involved in drug efficacy testing. Preliminary data from a study done in Kilifi were availed on the efficacy and effectiveness of ART-LUM to allay fears of effect of poor adherence on effectiveness (see Chapter 7). Sub-committees were formed to look at the various drug and non-drug issues. These committees were: therapeutic efficacy testing (TET); legal issues, guidelines and formulations; logistics, procurement and supplies; case management

(DOMC, 2004c). In the fourth meeting, the terms of reference of these sub-committees were defined and the need to monitor drug quality, to study registration requirements and procedures were reiterated (DOMC, 2004d).

The fifth DPTWG meeting was convened urgently against the backdrop of an impending GFATM deadline. The deadline for the GFATM 4th round of applications was the 5th of April and a decision had to be made on what the next first-line drug would be (see Table 2.6 for ACT international milestones). From the deliberations of the sub-committees, the two viable options were considered ART-LUM and AQ-AS. It was agreed that ART-LUM would be the first-line drug of choice for Kenya. It was agreed also that the Zambia example be followed, i.e. that the new policy be rolled out and data collected alongside implementation. Although AQ monotherapy was failing by day 28, it was felt that data on AQ-AS would be needed to justify the decision to use ART-LUM instead of AQ-AS, thus it was decided that the two be compared in the next round of testing and that WHO and the UK Department for International Development (DfID) would be approached for funding. Although concerns were raised about the high cost of ART-LUM, it was deemed the only option because any other ACT would have a limited Useful Therapeutic Life (UTL) as all had been used as monotherapies and already showed evidence of failure. Committees were called upon to revise existing guidelines and make recommendations on the best strategies for implementing the new policy to be presented at a National Symposium in April (DOMC, 2004e).

In the sixth DPTWG meeting, a need was expressed to write a position paper based on the deliberations of the sub-committees. The TET sub-committee expressed concerns about funding arrangements for the proposed efficacy studies and asked for more time to discuss this at a latter stage. The case management sub-committee raised a number of issues, i.e.

the need to harmonise proposed guidelines with IMCI; the management of malaria among pregnant women given that ART-LUM could only be used in the second and third trimester and only if there is no alternative; the likely interaction between ART-LUM and quinine; and the fact that only a 4- dose regime of ART-LUM was registered instead of the recommended 6-dose regime in Kenya. The committee was granted a one-day retreat to harmonise their findings. The guidelines harmonisation, advocacy and legal issues sub-committee stressed the need to learn from the change from CQ to SP in terms of drug sourcing, distribution, affordability, policy and legal issues, costs and quality assurance. It stressed the need for a staggered approach to policy change, intensive personnel training, and the involvement of the Pharmacy and Poisons Board (PPB). The logistics, procurement, and supplies sub-committee stressed the need to work closely with KEMSA in streamlining drug procurement in the public sector and Population Services International (PSI) in the private sector. The committee proposed to include some of its findings in the GFATM 4th round application (DOMC, 2004f).

In the seventh DPTWG meeting, the case-management sub-committee raised the need to use ACT in combination with good diagnostics to reduce unnecessary and inappropriate use of an expensive drug. It was also of the view that ART-LUM and AQ would not be used among pregnant women for Intermittent Presumptive Treatment (IPT). Instead, SP would continue to be used in the interim as the Centers for Disease Control (CDC) data suggested it was still effective. Lapdap® (chlorproguanil-dapsone) was not considered a good IPT option due to concerns about its safety raised by the WHO delegation. The committee also stressed the need to implement the policy in phases and to have consistent IEC messages for the members of the public. The logistics committee stressed the need to engage both KEMSA and MEDS in procurement and distribution (see Section 3.3.1 for AM procurement arrangements in Kenya) and the legal committee stressed the need to

monitor drug quality. Although drug quality was not seen as a problem in the interim since ART-LUM was to be sourced from a single supplier (Novartis Pharma AG), in the long term it would pose a challenge to case management if other products, similar in nature, came into the market (see Chapter 6). The efficacy committee stressed the need to monitor the new drug routinely and compile reports as it had done in the past for monotherapies. In terms of funding, there was need to have partners on board especially at the National Symposium. Overall, members agreed to speak with one voice at the National Symposium in Naivasha where the Minister was expected to issue a statement on the proposed policy change in Kenya (DOMC, 2004g).

The consultative process described above culminated in a 'National Symposium on Next Anti-Malaria Treatment Policy in Kenya' in Naivasha on 5-6th April 2004. At the symposium, the DPTWG sub-committees and other invited guests summarised their deliberations over the preceding months and possible solutions to the issues that were raised at these meetings. The Minister informed the gathering that, after negotiations with relevant bodies and development partners, Kenya had opted to change policy to the WHO recommended ACT and ART-LUM in particular as the first-line treatment for uncomplicated malaria (MoH, 2004b). The new policy was officially announced on April 25th 2004, coincident with Africa Malaria Day, in a speech delivered by Mr Francis Kimani, the Deputy DMS on behalf of the Minister at Kimbimbi sub-District Hospital in Kirinyaga (http://www.eastandard.net, accessed 07/12/04; http://nationmedia.com, accessed 07/12/04).

Table 2.6: International milestones in the push towards ACT therapy

Date	Event
October 1996 to date (White & Olliaro, 1996; White, 1999; Bloland *et al.*, 2000; Nosten & Brasseur, 2002; WHO, 2003c)	Epistemic community[11] argues for the rationale of using combination therapy (CT) in malaria (especially ACT) in the face of antimalarial drug resistance and rising malaria morbidity and mortality. Drugs in combination would reduce the chances of resistance to either of the components and thus increase the useful therapeutic life of the product (UTL). Cost is identified as one of the likely impediments to ACTs.
January 2002	Global Fund for Aids, Tuberculosis, and Malaria (GFATM) is launched to help cash-strapped African governments to roll back these major causes of morbidity and mortality using international funds.
16 January 2004	Initial rounds of GFATM funding termed as 'medical malpractice' by Attaran *et al.* (2004) in the Lancet because funds were approved for already failing therapies in some countries. This results in a flurry of correspondence to the Lancet for and against the GFATM.
June 2004 (Butler, 2004)	Following pressure from epistemic community above, GFATM agrees to allow countries, which had been allowed to purchase 'ineffective antimalarial drugs' in rounds 1-3 to redirect this to more efficacious drugs like ACT.
September 30-October 2 2004	GFATM reprogramming meeting held in Nairobi Kenya.

2.7.3 Players and power

Following the announcement of the policy change by the minister of health in April, another 'consultative process' seemed to evolve which affected the operationalisation of the policy change. Stakeholders took "for", "against" or "unconvinced" positions with regard to the new policy (Figure 2.9). Although these positions were not always explicit, they could be intuitively deduced from the interactions between the "for" and "against" camps with key MoH policy makers (the PS and DMS) who remained "unconvinced".

2.7.3.1 The "For" and the "Against"

The "for" group was championed by the DOMC in collaboration with the local malaria research community and its international epistemic counterpart. The effect of the latter on the swing to ACT has been demonstrated earlier (Table 2.6). Novartis Pharma AG, being

[11] Defined by Haas (1992) as "groups of actors with an authoritative claim to scientific knowledge within their sphere of expertise or the domain in which they operate" (op cit Lang, 2003).

the sole supplier of ART-LUM (Coartem®), stood to benefit from the new policy and its position was therefore intuitively clear. On the other extreme, were competitors of Novartis for market share of antimalarial drugs broadly. These included local manufacturers (like Cosmos Limited) whose position was explicit by way of direct representations to the PS and DMS or indirectly through their professional associations like the Pharmaceutical Society of Kenya (PSK) to reconsider the new policy. In an opinion letter to the PS dated October 6th 2004, copied to the DMS and the Chief Pharmacist, Cosmos Limited (the market leader in the manufacture of generic AQ in Kenya, see Section 5.3.4) suggested AQ as first-line policy and AQ-AS as second-line.

Multinationals like the Swiss Mepha Limited and the French Sanofi Synthelabo Limited launched "alternative ACTs" shortly after the policy change (an implicit position). Sanofi-Synthelabo launched AQ-AS (Arsucam® at USD 2.4 for an adult course and 0.7 for a paediatric dose) on April 8th 2004 shortly after Naivasha, and Mepha launched ART-MEF (Artequin® at USD 7.4 per adult treatment course) on October 1st 2004 (http://www.nationmedia.com, accessed 07/10/04). Both products were considered unsuitable for Kenya because the former contained AQ, a failing monotherapy and the latter contained mefloquine (MEF). Use of MEF has been associated with cross-resistance with halofantrine and reduced sensitivity to quinine (WHO, 2000b), making it unsuitable for use as monotherapy or in combination in East Africa where quinine is reserved for severe malaria. Nonetheless the Sanofi product raised "scientific eyebrows" because local newspaper reports and media houses quoted the Head of the DOMC as saying that AQ-AS was the new first-line policy in Kenya (http://www.nationmedia.com, accessed 10/04/04) an allegation that was seen as mischievous by the "for" group (Prof RW Snow and Dr W Akhwale, personal communication).

In a letter dated August 11th 2004 addressed to its members, the Pharmaceutical Society of Kenya (PSK) made its opposition to the new policy clear. PSK was opposed to dependence on donor finances in principle and more so for something as crucial as first-line antimalarial drug policy. It also maintained that the policy was at best vague and at worst unsuitable for Kenya. In addition, PSK cast doubts on the scientific evidence in support of ART-LUM (safety, efficacy) and specifically queried the safety of ART-LUM in children, the elderly and pregnant women. PSK pointed out possible interactions between ACT and quinine should patients fail to respond to ACT and require quinine in the course of therapy. Further, PSK argued that the new policy left out vulnerable sections of the population like children since there was no paediatric formulation of ART-LUM. Finally, PSK questioned the inclusiveness of the stakeholder consultative process leading to the policy change (PSK, 2004).

In a letter dated August 19th 2004, addressed to the Manager of the NMCP, Novartis Pharma AG argued that PSK's position was informed by economic considerations of its members who were largely drawn from the local pharmaceutical industry who were in turn concerned about losing market for their SP, AQ and artemisinin monotherapies in the light of the new policy (Dr. W Muiruri, personal communication).

2.7.3.2 The "Unconvinced"

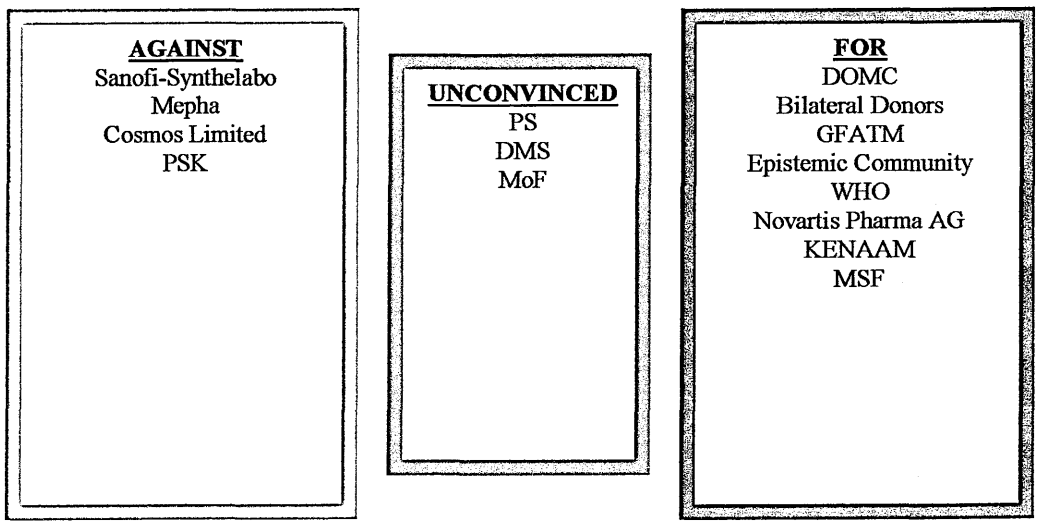
A key debate, which impeded the implementation of the new policy, was financial sustainability. ART-LUM is several times the cost of SP (Chapter 5) and could not be financed directly and solely by the GoK. Kenya successfully applied to the GFATM to finance the new policy and was granted approximately US$ 82 million (on July 1st 2004) for the first two years of the programme (http://www.theglobalfund.org, accessed 08/10/04). However, as with all GFATM awards, funding is pegged to achievement of

short-term performance targets. This caused reluctance among top decision makers in the MoH to fully commit to implementation of the new policy. The MoH therefore requested assurances from the GFATM that the new policy would not run out of money mid-stream. The GFTAM arranged for a meeting in Nairobi between September 30th and November 2nd 2004 to clarify funding issues. Although no formal minutes were available, attendees reported that GFATM was non-committal.

The ministry was also concerned about access to ART-LUM in the private sector, where the drug is not offered at a concessionary price by the manufacturer and where a substantial proportion of Kenyans seek treatment. In addition, there are regulatory issues (for instance the need to deregulate ART-LUM from prescription-only medicines to the general sales list), which needed to be addressed to widen access to ART-LUM in the private sector (see Section 3.4.4 for more on the regulatory issues). Thus, on September 14th 2004, the DMS requested stakeholders to come up with another position paper on these issues to strengthen his case in advocating for the new policy at the ministerial level (MoH, 2004c). At the time of writing this thesis, the implementation of the new policy remained unclear, and specific recommendations on the use of ART-LUM in the private sector had not been provided to the DMS. Further, the implementation of the proposed policy has been put in a quandary by a global shortage of ART-LUM. The WHO issued a statement on November 8th 2004 to the effect that only a third of the estimated 60 million doses global need for ART-LUM could be met by Novartis, and that most of these doses will only be delivered towards the end of 2005 (http://mosquito.who.int/rbm/Attachment/20041108/pr8nov2004.htm). The WHO thus recommended that countries increase procurement of their second-line drug; an advice that is unlikely to be heeded in Kenya since the second-line drug is oral quinine (both old and

proposed policy), a drug that is regarded as a reserve drug (and whose increased use will most likely meet stiff opposition).

Figure 2.9: Position map of important stakeholders regarding implementation of ART-LUM, the new first-line AM policy in Kenya.



2.8 Summary

Kenya is a poor developing country with a declining health status of its population since the early 1990s. In the same period, key economic indicators have been on the decline with negative growth being registered in the year 2000. In addition, the country witnessed momentous political changes, especially in the past two years, and is still in a state of political transition. This chapter reviewed the malaria situation, treatment seeking for fevers and for malaria, antimalarial drug resistance, and drug policy changes in the country in the context of this socio-economic and political environment.

The review showed that malaria is a disease of major public health importance in Kenya predominantly affecting children below the age of five and pregnant women. The chapter also demonstrated that Kenyans seek treatment from a variety of sources and that almost half of all fevers are self-medicated with drugs at home or those sourced from the retail

sector. Malaria is taking its toll on Kenyans against a backdrop of declining efficacy of previously effective and cheap therapeutics like CQ and SP.

Increasing resistance to first-line antimalarial drugs in Kenya has resulted in a policy change twice in the past decade: first from CQ to SP in 1998, then from SP to ART-LUM in 2004. The work described in this thesis started at a time when SP and AQ monotherapies were showing decreased efficacy but there was no suggestion of changing policy, while the thesis was written at a time of precipitous decline in SP efficacy and emerging evidence of decline in AQ efficacy by day 28 in Kenya and in the sub-region. Internationally, the thesis was written amidst a push towards ACT by an increasingly vocal malaria epistemic community and at a time when there was a stated WHO policy of making sure countries in the region changed failing first-line AM monotherapy to the more efficacious, albeit expensive ACTs. The chapter demonstrated that from the available ACTs, Kenya had one option: ART-LUM, which was adopted following a national consultative process that included national and international stakeholders. The evidence also suggested that AM drug policy change in Kenya was not a linear, predictable and scientific process, but an iterative, both scientific and political one where powerful groups or individuals could impede change.

The proposed policy has not been implemented, largely due to concerns on financial sustainability. International funds through GFATM would probably have allayed these fears and kick-started the process, but the Round IV agreement has not been signed to free up necessary monies to procure ART-LUM in appreciable quantities (although such procurement would now run into supply difficulties as mentioned in 2.7.3.2). Further, the proposed staggered implementation of the policy, concentrating first on the formal sector and slowly progressing to the private sector, has left the latter unsupported and with no

obvious direction. Ultimately, the proposed engagement of the private sector requires careful strategic leadership of the DOMC, formative research, and broadening involvement of stakeholders. Many of these stakeholders have, as shown in this chapter, been adverse to ART-LUM, forming the "Against" lobby-most notably the local pharma industry. How to bring the private sector and its suppliers into the future drug policy implementation will pose a large challenge. The likely scenario of ignoring this sector in terms of community effectiveness of interventions is discussed in Chapter 8.

CHAPTER 3:

Legal and policy framework for the regulation of antimalarial drugs in Kenya

3.1 Introduction

The regulation of the health sector in general and that of the pharmaceutical sector in low- and middle-income countries (LMICs) has been studied in a number of countries (Stenson *et al.*, 1997; Hongoro & Kumaranayake, 2000; Kumaranayake *et al.*, 2000; Meng *et al.*, 2000; Soderlund & Hansl, 2000; Soderlund & Tangcharoensathien, 2000; Stenson *et al.*, 2001; Kumaranayake *et al.*, 2003). Soderlund & Tangcharoensathien (2000) propose that regulation of the private sector in LMICs in general can be conceptualised as occurring in phases of regulatory maturity: pre-regulation, "paper" regulation, mature regulatory response (consisting of appropriate, focused regulation, regulatory capture or over-regulation) and deregulation. In the pre-regulation phase, private sector activity is either banned or ignored, for instance in China (Meng *et al.*, 2000), because this is seen as an admission that the government is unable to provide essential services to its citizens. In the "paper" regulation stage, legislative efforts are made to regulate private health care provision, but such efforts are hardly enforced. This best describes regulation of the private health care providers in most of sub-Saharan Africa (Hongoro & Kumaranayake, 2000; Kumaranayake *et al.*, 2000; 2003) and some parts of south-east Asia (Stenson *et al.*, 1997; 2001). In the third phase, i.e. mature regulatory response, the ideal situation is when governments liase with the private sector to find out what the challenges are and seek appropriate solutions for those challenges. In some cases however, the governments either end up serving the interests of the private sector more than those of public health (regulatory capture) or end-up over-regulating the private sector. In some instances, regulatory outcomes are deemed adverse, resulting in calls for de-regulation as was the case of the South African health insurance industry in the 1980s (Soderlund & Hansl, 2000).

With regard to drug regulation, drugs are an essential health commodity and need to be regulated to save lives and improve health. Drug regulation is achieved by way of legal and policy provisions that set up the structures and processes that are needed to ensure public health. Contemporary drug regulation involves a number of tasks which include licensing and inspection of premises and professionals, licensing and inspection of manufacturers, drug registration and post-marketing surveillance (Quick *et al.*, 1997). Theoretically, the drug registration process, by which national governments approve (or reject) a drug for commercialisation and marketing, is the gateway to drug supply in a country.

This chapter seeks to examine how antimalarial (AM) drugs find their way into the market by way of the drug registration process in Kenya and how they are regulated thereafter. Not only does AM drug regulation affect the level at which AM products are used (by way of drug scheduling) thus affecting access to much needed therapy in Kenya, but it also affects overall drug effectiveness. A poorly regulated system will most likely result in the presence of sub-standard drugs in the market (Chapter 6), which reduce the effectiveness of the products used to treat malaria (Chapter 7) and may lead to patient complications or death. Newly registered AM products are used to demonstrate the process, criteria and post-marketing surveillance for drugs under ordinary use in Kenya. This is done by way of a literature review, supplemented by interviews with key informants to demonstrate the view and experiences of a cross-section of stakeholders on drug regulation in Kenya.

3.2 Methods

A mixed-model comprising interviews and documentary review was used to gather data on drug regulation in Kenya (Abraham & Lewis, 2000; Lang, 2003). A thorough search of the literature on drug regulation was undertaken. This was followed by semi-structured interviews with key informants in academia, industry and the Pharmacy and Poisons Board

to supplement information gathered from published sources and reports. Although there are many stakeholders in drug regulation, the key ones are industry (regulated), the drug regulatory authority (regulator), and academia. Apart from playing a key role in drug discovery and development, academics also sit on advisory boards that make regulatory decisions. In Kenya for instance, the PPB has a Committee for Drug Registration (CDR) on which a member of the Faculty of Pharmacy, University of Nairobi, represents members of academia. Secondly, it is also common for academics to provide consultancy services to industry.

A complementary qualitative approach (complementary to literature review) was used because of its obvious advantages. Not only is it a rapid way of collecting data, but also it is known that what is documented is not what always happens on the ground. For instance although drugs are registered on the basis of safety, quality and efficacy in most countries, there have been several reports of substandard drugs circulating in the markets of sub-Saharan Africa (Chapter 6). Furthermore, unregistered drugs also circulate in these markets (Chapter 5). In addition, the qualitative approach would provide an understanding of the views and experiences of the people involved in formulating and/or implementing regulatory decisions and thus help explain the context in which drug regulation takes place. Informants and companies were assured of their anonymity or that of their products to ensure cooperation, therefore no reference is made to specific informants or products in this thesis (Table 3.1). Instead, a coding scheme consisting of the country (e.g. KEN for Kenya), sector (REG for regulator) and interviewee (1, 2, etc) has been used and AM1 and AM2 used to denote the two antimalarial products used to illustrate process and criteria for antimalarial drug registration.

Table 3.1: Persons and organisations whose views and experiences on drug regulation in Kenya were sought in 2004

Study Site	Academia	Industry	Regulator
Kenya	Senior Researcher in Malaria and Clinical Pharmacologist Senior Lecturer in Pharmaceutical Chemistry	Regulatory Affairs Manager, Large Scale Local Manufacturer of branded generics	Senior Regulator in Drug Registration, Pharmacy & Poisons Board (PPB). Junior Regulator, Drug Registration, Pharmacy and Poisons Board, Kenya
Piloting	Supervisors*	Regulatory Affairs Manager of a Large Scale Importer and Distributor of pharmaceuticals in Kenya.	Senior Regulator, Pharmacy and Poisons Board, Zambia

* Background interviews were also conducted with Kenyan supervisors.

3.2.1 Procedures

Potential interviewees in the various sectors were identified in consultation with PhD supervisors and contacted for permission to interview them at a convenient date. Interviews were mostly conducted via telephone in a standardised manner and were tape-recorded (with the consent of the interviewees). The use of telephone was occasioned by time and resource constraints. Interviewee confidentiality was maintained at all times. The interview schedules were developed further by brainstorming with experienced people outside the target group and piloted in a similar group to the target group. The definitive interview schedules (see Appendix I for an example) were e-mailed to the final group of respondents and a follow-up appointment arranged for the interviews. The advantages of telephone interviews rest on their relative anonymity and the ability to talk to respondents in widely varying geographical locations. Telephone interviews also tend to be shorter and proceed in a brisk, business-like manner. Doubts have been raised about the quality of telephone interviews compared with face-to-face interviews (Donovan *et al.*, 1997), but these have largely been discounted (Korner-Bitensky *et al.*, 1991; van Wijck *et al.*, 1998; Greenfield *et al.*, 2000).

3.2.2 Qualitative data analysis

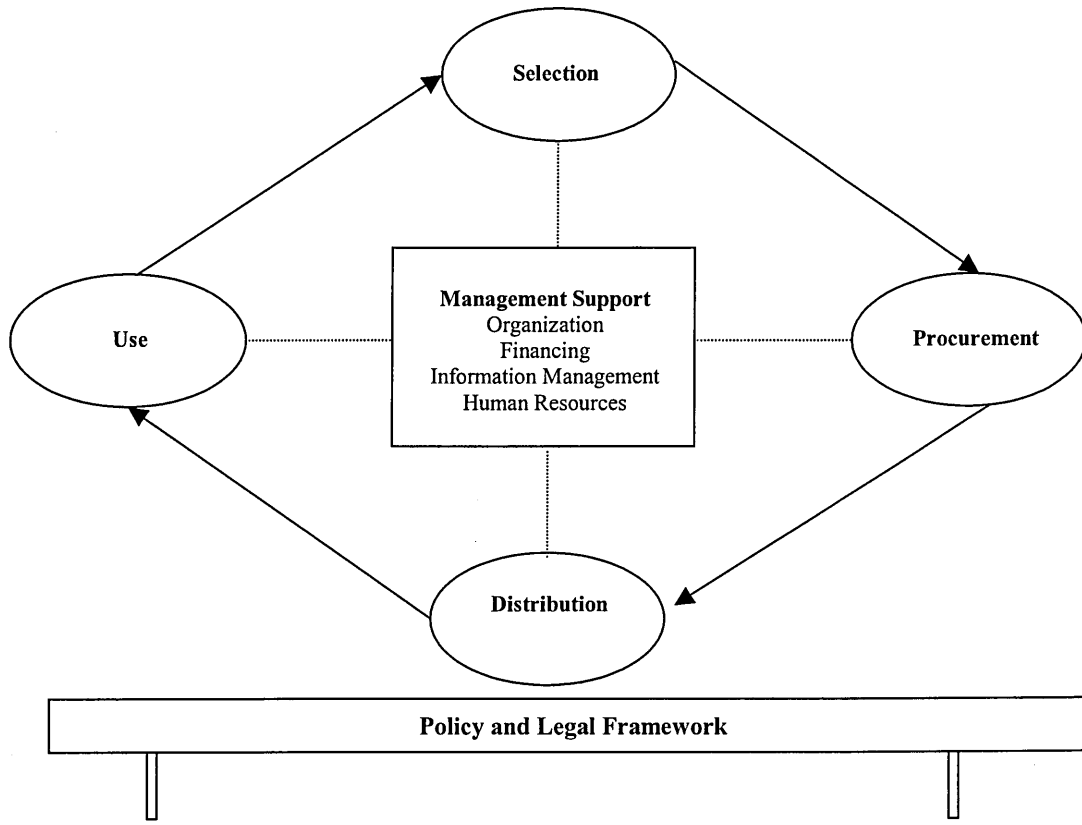
Data analysis followed a Framework Analysis method, popular in health-related research and developed in the context of applied policy research. Analysis involved the following key stages as suggested by Ritchie and Spencer (1994): familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation.

1. Familiarisation: interview transcription, reading and re-reading
2. Identifying a thematic framework: development of coding framework both from *a priori* issues in drug regulation and from emergent themes from interviews
3. Indexing: applying thematic framework to the data using numerical or textual codes
4. Charting: developing thematic charts
5. Mapping and interpretation: searching for patterns, associations, concepts and explanations in data for observations

3.3 Results

The flow of medicines in Kenya and the place of regulation in medicines control can best be visualised by way of the drug management cycle which has the following key elements: selection, procurement, distribution and use (Figure 3.1). The four arms of the drug management cycle require management support and also rest on a policy and legal framework (Quick *et al.*, 1997).

Figure 3.1: Elements of the drug management cycle (Quick *et al.*, 1997).



3.3.1 Drug management cycle in Kenya: the four arms

In Kenya, drugs for procurement for the government public sector are selected from the Kenya Essential Drugs List (KEDL). This list was first published in 1981 (revised twice thereafter, in 1992 and in 2003) and based on the WHO model list of essential drugs, developed for all levels of healthcare (MoH, 1993). Drugs for the government sector were originally procured by an independent procurement agency (Crown Agents) by way of an annual international open tender (occasionally through restricted tenders), although the Kenya Medical Supplies Agency (KEMSA) is increasingly taking this role (Interview with KENAC1, 19/03/04). KEMSA is a government parastatal[12] which replaced the former Medical Supplies Coordinating Unit (MSCU) of the Ministry of Health (MoH) and its

[12] The term "parastatal" in Kenya refers to a semi-autonomous body that receives part of its funding from the government, but also has a mandate to generate its own funds. It is synonymous with "trading-fund status" in British parlance and such a body can thus sue or be sued.

mandate includes procuring, warehousing and distribution of drugs to government facilities. Three departments within KEMSA procure drugs and medical supplies. These are the office of the pharmacist-in-charge that procures pharmaceuticals; the supplies department, which procures non-drug supplies; and a laboratory manager who procures laboratory reagents and equipment. These three departments are advised by a procurement committee, which meets twice a month. Decisions are passed to the Permanent Secretary in the MoH who is part of a Ministerial Tender Board. However, Kenyatta National Hospital, the national referral hospital (which is a parastatal of its own), is not part of this pooled procurement system and does its own procurement. Further, AM drugs are procured on behalf of the government by a consortium composed of KEMSA, Crown Agents, the German Technical Cooperation Agency (GTZ) and John Snow Inc. (JSI), established in response to management prerequisites for monies disbursed by the Global Fund for AIDS, TB and Malaria (GFATM) (Tetteh & Mwangi, 2004).

After drugs have been procured by KEMSA from a given supplier, they are delivered to the central warehouse in Nairobi by the suppliers or to eight regional warehouses from where the drugs are distributed to the rest of the country (Figure 3.2). Nairobi and its adjacent districts (e.g. Makueni, Kajiado, Machakos) obtain their drug requirements from the central warehouse whereas other districts obtain drugs from the regional warehouses in the provincial headquarters. Provincial General Hospitals (PGHs) and District Hospitals (DHs) obtain their drug supplies either from the central or regional warehouses, depending on their location. Health Centres and facilities at the lower level of health care receive their drug requirements from the DHs. In addition to the central and regional warehouses, KEMSA manages warehouses for vertical programmes such as the Kenya Enhanced Programme for Immunization (KEPI) and the National Leprosy and TB Programme (NLTP) (Tetteh & Mwangi, 2004).

Although now in a transition, drug distribution to the government health facilities is predominantly through a kit or the so-called "push" system. Depending on the level of care (primary, secondary, tertiary), different hospitals or clinics will receive different kits. Table 3.2 shows examples of AM drugs contained in government kits for the financial year 2001/2002 (Dr C Kandie, personal communication). Not all AM drugs are supplied by way of kits. AQ for instance is supplied loose to all facilities. Also, AM drugs to PGHs, DHs and sub-district hospitals (SDHs) are supplied loose in line with the fact that since July 2003 KEMSA has been operating a requisition-based or "pull" system for these types of facilities (Tetteh & Mwangi, 2004). At present, KEMSA is undergoing some reorganization and a pilot study of a fully decentralized drug supply system is underway in Nyamira District. The key elements of this strategy are: giving the districts seed money (Revolving Drug Fund), districts determining their own drug requirements, then purchasing these from whatever source at competitive prices, all part of the health sector reform predicated on decentralization and taking services closer to the people (Interview with KENAC1, 19/03/04).

Table 3.2: Antimalarial drug contents of Government of Kenya kits for the financial year 2001/2002 (Dr C Kandie, personal communication).

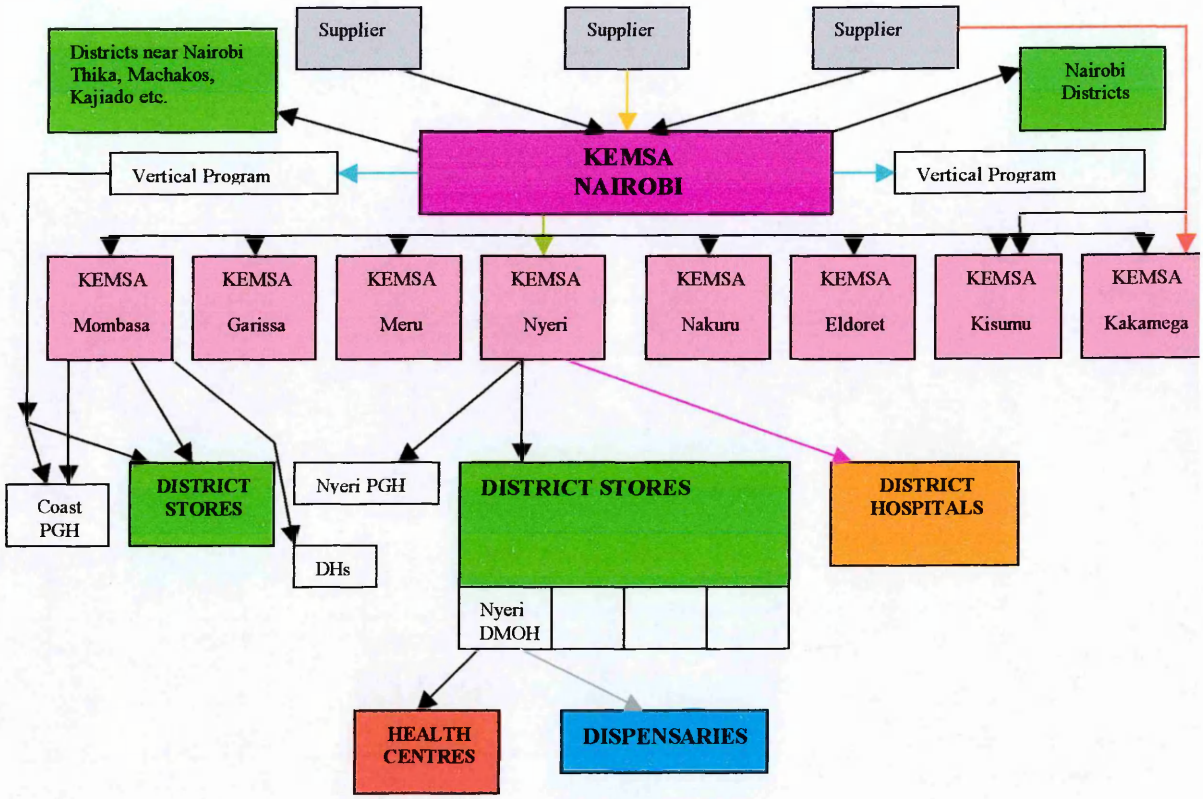
Kit Type	Item Description	Unit Pack	Quantity
Dispensary Ration Kit IIA	Sulfadoxine/pyrimethamne tablets USP (500:25mg)	1000	2
Dispensary Ration Kit IIB	Sulfadoxine/pyrimethamne tablets USP (500:25mg)	1000	1
Health Centre Ration Kit IIA	Sulfadoxine/pyrimethamne tablets USP (500:25mg)	1000	3
Health Centre Ration Kit IIB	Sulfadoxine/pyrimethamne tablets USP (500:25mg)	1000	1
Out-Patient (OPD Standard Kit)	Sulfadoxine/pyrimethamne tablets USP (500:25mg)	1000	4
	Quinine Bisulphate Tablets BP 300mg (film-coated)	1000	3
	Quinine Paediatric Oral Drops BP/USP 10mg/drop (20%)	15 ml bottles	10
Hospital In-Patient Kit	Quinine Dihydrochloride Injection BP 300mg/ml	2ml ampoules	500

The mission and non-governmental organisations that provide substantial healthcare in Kenya (Chapter 2) largely follow a similar selection and procurement system, but may differ in how they distribute drugs. For instance the Mission for Essential Drugs and Supplies (MEDS), which supplies drugs and medical appliances to the mission sector, uses a "pull" system whereby hospitals and clinics requisition for what they need as opposed to all hospitals or clinics of a given level of care receiving a uniform kit (Quick *et al.*, 1997).

Drug use in Kenya is ideally controlled by the use of national standard treatment guidelines and for some specific diseases categories like malaria there are, in addition, specialised treatment guidelines (MoH, 1994a; DOMC, 1998). Details of antimalarial drug use in Kenya are covered in Chapters 2 and 4.

Whilst it has been possible to describe drug supply in the mission and GoK sectors in detail above, the private sector poses a challenge. Not much is known about drug supply in this sector except that 1) almost half of essential drugs are supplied by this sector (Foster, 1991), and 2) that selection, procurement, distribution, and use follows market forces (Interview with KENAC1, 19/03/04). Chapter 5 partially redresses this knowledge gap, but as will be shown, there is scope for more formative research.

Figure 3.2: KEMSA government of Kenya central drug distribution system (Tetteh & Mwangi, 2004).



Key (Arrow colour codes)

→	KEMSA warehouses for vertical programs e.g. KEPI, NLTP, NASCOP, DARE
→	Sometimes KEMSA instructs suppliers to supply directly to Regional Depots
→	Vertical programs do their own distribution from KEMSA Nairobi. Sometimes deliver to District and Provincial Hospitals
→	Lead time of 6 months is from Advertisement of Tender to receiving in KEMSA Nairobi
→	Continuous supply. Lead time is about 1 week
→	Monthly supply

3.3.2 Drug management cycle: the policy and legal framework for drugs in Kenya

The Policy framework for drugs in Kenya is espoused in a Kenya National Drug Policy (KNDP) document, published in 1994. Inspired by the WHO essential drugs concept, KNDP's main goal was to "...use available resources to develop pharmaceutical services to meet the requirements of all Kenyans in the prevention, diagnosis and treatment of diseases using efficacious, high quality, safe and cost effective pharmaceutical products.". This goal was to be achieved via specific objectives, which captured five key elements for both human and veterinary medicines: availability, affordability, rational use, quality and local manufacture of medicines in Kenya (MoH, 1994b). An implementation programme- The Kenya National Drug Policy Implementation Programme (KNDPIP)-funded by both the government and development partners (mainly the Dutch Government) was quickly put in place. The national drug policy was to be implemented in phases and backed up by legislative changes to existing laws on medicines in Kenya. A mid-term review of KNDPIP was completed in February 1998 and three main components identified as being of immediate priority and relevance to reform the pharmaceutical sector (PPB, 1999). These were:

1. Drug regulation and control
2. Drug selection and procurement
3. Education and training

Although the success of the KNDIP is debatable, it has nonetheless given birth to a number of guidelines which it is envisaged will receive legislative backing with the revision of the Pharmacy and Poisons Act, Chapter 244 of the laws of Kenya (Interviews with KENAC1, 19/03/04). Examples of these guidelines are those on drug donations (MoH, 2001b), safe disposal of pharmaceutical waste (MoH, 2001c), and clinical guidelines (MoH, 1994a).

The KNDP proposed to promote the same principals of drug management in the private sector, but these obviously have not been achieved as evidenced by 1) high and inequitably priced essential drugs in this sector (Chapter 5); 2) importation of a substantial part of essential drugs (Chapter 5); and 3) the presence of sub-standard products in the market (Chapter 6).

3.3.3 History of drug regulation in Kenya

Like most other Commonwealth countries, drug laws, and indeed other laws in Kenya are a legacy of British colonial rule. Kenya attained her independence from Great Britain on June 12th 1963.

In the early days, the colonial authority introduced training courses for Kenyans in compounding and dressing of wounds. 1927 saw the introduction of a two-year course leading to the African Compounder Certificate "A". A course for the dressing of wounds which was in operation as far back as the First World War later matured into nursing training (Ombega, 1999). 1933 saw the commencement of the Dangerous Drugs Act which sought to regulate "...the importation, exportation, manufacture, sale and use of opium and other dangerous drugs" (GoK, 1992). On May 1st 1957, the Pharmacy and Poisons Act Chapter 244 of the Laws of Kenya came into operation and has been the cornerstone of drug regulation in Kenya ever since. Drug registration procedures, however, did not begin until much later (April of 1982) after the Ministry of Health gazetted the Pharmacy and Poisons (Registration of Drugs) rules 1981 (PPB 1996). Apart from miscellaneous amendments from time to time (e.g. revision of penalties), the Pharmacy and Poisons Act has not undergone a comprehensive and extensive review (Ombega, 1999).

3.3.4 Key drug legislation and associated structures

In theory, there are many acts and laws dealing with drugs and poisons in Kenya. Drugs and poisons are controlled by the Dangerous Drugs Act, the Food Drugs and Chemical Substances Act, the Pest Control Act, among others. In addition, there are acts of parliament, which regulate the various groups of professionals who handle drugs and poisons on a day-to-day basis e.g. the Medical Practitioners and Dentists Act, the Nurses Act, and the Clinical Officers Act. In practice however, drugs in ordinary use (e.g. the sale and distribution of AM drugs) are largely covered under the Pharmacy and Poisons Act 1957. This legislation and its related administrative structures are covered in detail below.

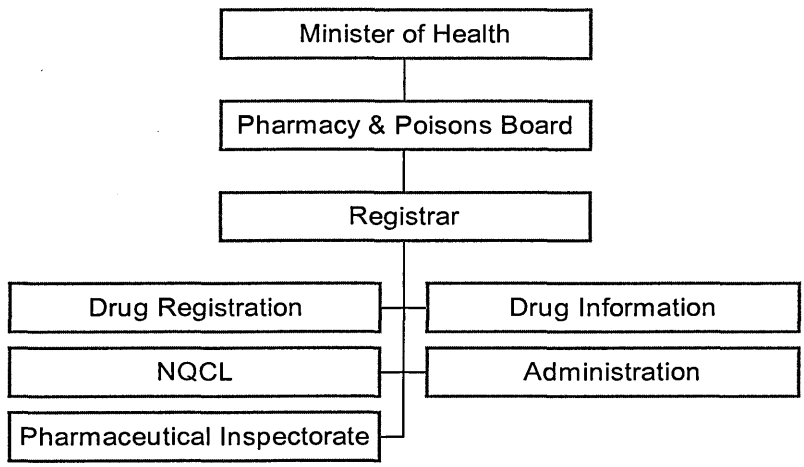
3.3.5 Pharmacy and Poisons Act 1957 and the Pharmacy and Poisons Board (PPB)

The mission of the Pharmacy and Poisons Board (PPB) is "....to implement the appropriate regulatory measures to achieve the highest standards of safety, efficacy and quality for all drugs, chemical substances and medical devices, locally manufactured, imported, exported, distributed, sold, or used, to ensure the protection of the consumer as envisaged by the laws regulating drugs in force in Kenya...". The PPB was established by the Pharmacy and Poisons Act 1957, which was enacted just before independence. In its current form, the PPB is part of the Pharmacy Department of the MoH. At the top of the hierarchy is the Minister of Health, followed by the PPB. In line with its broad functions, PPB operations are divided into five main sections as shown in Figure 3.3. The Registrar is in direct control of all five sections. Although a separate office, the Registrar doubles up as the Chief Pharmacist (CP) in Kenya. The PPB became a body corporate in 1993 and can generate (and use) its own funds from its regulatory activities. In addition, the PPB receives salaried civil servants from the MoH to run some of its operations.

As it is currently constituted, the PPB members comprise the following:

1. Chairman (Director of Medical Services, MoH),
2. Registrar (CP) who acts as the Secretary
3. Director of Veterinary Services,
4. Pharmacists (4) nominated by the Pharmaceutical Society of Kenya (PSK) of whom one is from the Civil Service, one from Community Pharmacy, one from the Pharmaceutical Industry and one from academia (a representative from University of Nairobi's Faculty of Pharmacy)
5. Pharmaceutical Technologist

Figure 3.3: Organisational Structure of the Department of Pharmacy in the Ministry of Health, Kenya (MoH, undated).



The Pharmaceutical Inspectorate department monitors and evaluates industry compliance with the WHO GMP guidelines by regularly inspecting pharmaceutical manufacturing plants. Currently there are about 90 pharmaceutical companies (Odhiambo, 1999), approximately 40 of which manufacture products locally. The department was set up under the KNDIP in 1994, but started its operations in May 1999. Inspection findings are presented before the PPB for action; concerned industries are also sent copies of the report

and given between a month and a year to correct anomalies, depending on their nature[13]. MoH drug inspectors carry out inspection of drug distribution channels, although the Pharmaceutical Inspectorate is also mandated to do so. In reality, inspection focuses mainly on the urban centres that are readily accessible.

The National Quality Control Laboratory (NQCL) undertakes quality checks of drugs mostly for the purposes of drug registration, although it also receives samples from private companies and individuals. The laboratory is also mandated to monitor drug quality post-registration. The CDR at the PPB forwards samples to NQCL for analysis. CDR is the single biggest client of the laboratory and because of constraints at NQCL (financial, personnel), decisions as to which samples should be taken for a quality check are *ad hoc* and based on the committee's judgment. "Suspect" drugs (incomplete documentation, poor product aesthetics) or "critical" drugs (AM drugs, anti-TB, anti-epileptics, and Anti-Retrovirals) are theoretically given priority for quality checks. NQCL is a body corporate, which in theory is the technical arm of the PPB, however, its legal standing is not entirely clear. The laboratory gets personnel seconded from the MoH (mostly pharmacists) and employs technicians from its own financial vote.

3.3.6 Drug registration: process and criteria

Registration of drugs in Kenya came into effect in April 1982, after the MoH gazetted the Pharmacy & Poisons (Registration of Drugs) rules 1981, under the Pharmacy & Poisons Act chapter 244, Laws of Kenya (PPB, undated). The PPB registers all products intended for the Kenyan market, as well as those for export using product quality, safety, and efficacy as the three most important criteria. Although not yet operationalised, the KNDP

[13] Anomalies are categorised into those Requiring Urgent Attention (RUA, given between one to three months e.g. lack of Standard Operating Procedures or Quality Control laboratory), Requiring Attention (RA, given four to nine months e.g. use of outdated analytical methods) and Requiring Consideration (RC, given up to a year e.g. poor positioning of stores).

also proposed specific medical need, proposed wholesale and retail prices and unique characteristics (life-saving drugs and orphan drugs) as additional important criteria to consider when registering drugs (MoH, 1994b).

The PPB has committees of experts in various disciplines including pharmacology, pharmaceutics, pharmacodynamics, pharmaceutical analysis, industrial pharmacy, dermatology, and veterinary medicine. Drug registration is handled by the CDR. The committee vets all documentation accompanying the application for registration of a drug. Applicants fill in six copies of a standard form, submit six commercial packs of the candidate drug (the smallest) and sufficient documentation to back their claims. They also pay a fee of USD 500 for Kenyan products and USD 1,000 for imported products per application.

The next step is the vetting process that is primarily confined to scrutiny of documentation supporting the drug in terms of safety, quality, and efficacy. In addition, the packaging or aesthetics of the product are also considered. When documentation is deemed inadequate, applicants are requested to supply additional information. Successful applicants are given a letter of approval, which allows them to market their product in Kenya, pending gazetting and the final letter of registration. Registration is valid for 5 years, after which a re-registration is sought from the CDR for another 5 years and so on *ad infinitum*. Registered drugs are scheduled into two broad parts (each with sub-parts): part I poisons which can only be dispensed by a registered pharmacist or part II poisons which may be dispensed by a registered pharmacist or a pharmaceutical technologist (Table 3.3). Drug schedules, however, are not adhered to in practice and it is not uncommon to find POM drugs like AQ sold OTC (Chapter 4).

Table 3.3: Drug schedules in Kenya (MoH, 1994b).

Poison	Schedule
Part I	Schedule I-These are Prescription Only Medicines (POM) and require a prescription from a registered doctor (human or veterinary) or dentist. They may however be dispensed by a registered pharmacist in small quantities in emergencies i.e. where an authorised prescriber is unavailable.
	Schedule II-These are Pharmacy Only Medicines and require a prescription from an authorized prescriber.
Part II	Schedule III-Dispensed by registered pharmacists without a prescription or by a pharmaceutical technologist on prescription.
	Schedule IV-Over the Counter (OTC) medicines. Can be sold on authorized outlets without a prescription.

Imported drugs intended for registration in Kenya must be accompanied by a certificate of free sale or certificate of pharmaceutical products (CPP) from the country of origin as proof that the products are fit for human use. In addition, importers are required by law to have an import licence as stipulated in Cap 244 and also fill the necessary import declaration forms per consignment (GoK, 1989).

3.3.7 Post-marketing surveillance: safety, quality, and efficacy.

There is no functional post-marketing surveillance of medicines in Kenya. Product quality can theoretically be monitored and indeed NQCL is mandated to do so, but due to financial and personnel constraints, this has not been possible in the past:

> **Interviewer**: And are all [drug] products taken for ...for quality check to the national quality control laboratory [NQCL] or are there certain products, which are taken there?
> **KENREG2**: Not all of them because there are quite a number; they [NQCL] would not cope. We just take the problematic products like antimalarials, anti-TBs and some antibiotics, carbamazepines and quite a number ...of those we think will require...by looking at it you can actually tell this one should go to the lab. And if there is a new company from India or elsewhere [whose products] we don't know the trend of the quality, we send for analysis (Interview with KENREG2, 02/08/04).

There is no functional mechanism for monitoring safety or efficacy of medicines in Kenya either (interviews with KENAC1, 19/03/04; KENAC2, 07/07/04; KENIND, 30/06/04;

KENREG1, 05/07/04; KENREG2, 02/08/04). However, some disease specific programmes like the National Malaria Control Programme (NMCP) do limited monitoring of the efficacy of antimalarial drugs through a regional network for monitoring malaria therapy- the East African Network for Monitoring Antimalarial Therapy (Chapter 2). Further, there is no institutional framework for evaluating drug effectiveness in routine clinical use in Kenya; only limited efficacy testing (not effectiveness) is done and only for specific disease categories like malaria (Chapter 2).

3.3.8 Views and experiences of industry, academia, and the PPB on drug regulation

3.3.8.1 Process and criteria for drug registration

In Kenya, product dossiers are submitted to the PPB, which forwards these to a committee of experts that evaluates the dossier for registration (CDR). The PPB lacks its own internal capacity for product evaluation; it relies entirely on expert advice:

> **KENREG1:** ...We normally have ... a drug registration committee, this is a committee of experts involving people who have expertise in pharmaceutical areas, others have expertise in clinical areas. Now, the application is in such a way that the pharmaceutical documentation will be evaluated by these pharmaceutical experts and the clinical documentation evaluated by the clinical experts. They will be able to make their comments and if need be that more information be submitted then they are able to communicate and send to the applicants. During the evaluation process, depending on the product, the samples may also be submitted to the laboratory [NQCL] for evaluation where the analysis has to be carried out. Now, depending on the outcome of both the documentation and the analysis, that is the time whatever comes out of that is what the applicant is normally told. Now, in the event that all of them are satisfactory, then the product is evaluated...recommended for registration (Interview with KENREG1, 05/07/04).

> **KENREG2:** ... ...we have a committee on drug registration [CDR] and we have a chairman who is a medical doctor, right now. Then that committee looks at the documents [dossier], which have been submitted, and then they come up with their comments, which we take as the secretariat. There are three categories: either a product is deferred waiting various clarifications which we write to the company to bring more responses, the product can be recommended for registration to the Pharmacy and Poisons Board and the product can also be rejected if it does not fulfil the criteria for drug registration (Interview with KENREG2, 02/08/04).

Antimalarial drugs and other drugs perceived to be important to public health are given priority in the regulatory pipeline than others i.e. a fast track mechanism exists for some products:

> **Interviewer:** And on an average how long does the process...the registration process take?
> **KENREG1:** Now, when a product [licence] is applied for, there is normally some time taken before the document is evaluated ...on average, that takes around ...between... around six months on average, even though for priority products, like HIV preparations...antiretrovirals, we have a fast track [system] in place whereby within two to three months the product will have been evaluated...
> **Interviewer**: And what is the rationale for fast tracking some products and not others?
> **KENREG1:** ...fast tracking some products is because ...for this particular market, the three indications ...malaria, TB and HIV are considered to be contributing to a lot of the disease burden and ...there is always a lot of pressure to be able to have as many preparations as possible for this indications and it's always been the Ministry's policy also to try and fast track products for this particular indications (Interview with KENREG1, 05/07/04).

It is also accepted that safety, quality, and efficacy are the criteria on which drug registration is based in Kenya. However, there is a perception that the process and criteria are not rigorously enforced. This is mostly explained in terms of little resources available to the PPB. This view however is not universal and some interviewees were of the opinion that there is an overarching structural problem with drug regulation in Kenya ranging from lack of independence of the PPB, deficiencies or contradictions in the legal framework for drug regulation, lack of an effective post-marketing surveillance for drugs, inadequate penalties imposed on those in contravention of the drug laws, to lack of political will to enforce the letter of the law. An oft-repeated example is that of police officers with scant knowledge of pharmaceuticals doing drug inspections (Interviews with KENAC1, 19/03/04; KENIND, 30/06/04; KENAC2, 07/07/04).

3.3.8.2 Illustrative case studies of registration of AM drugs, the case of AM1 and AM2

This section summarises the salient points for selected AM drugs used to illustrate process and criteria and perceptions of the various players in the interviews. Although there were

other products scheduled to be reviewed before it, AM1 (from a multinational company) was put on the priority list in Kenya since it was for malaria. However, the process took longer than would have been the case since the NQCL did not have the required chromatographic column for analysing the product (Interview with KENREG1, 05/07/04). In addition, AM1 was the first product in Kenya to make an electronic submission for registration (Interview with KENREG2, 02/08/04). The product took about six to eight months to be registered (Interview with KENREG1, 05/07/04).

> **KENREG1:** ...we put it [AM1] among the list of priority products because it is an anti-malarial and because by the time it came we had already done scheduling for the next several weeks; but we put it on line so that it could definitely be in queue for evaluation. Now after ...once its time came it was evaluated. It was also sent for analysis because ...for...that is what we do with all anti-malarials, anti-TB's and any HIV preparations that the products have to be evaluated. What happened... the problem that arose is that ...the laboratory did not have...could not be able to analyse the product because in the analysis of the product it required a special column and ...what happened is that ...it delayed the process of registration because the documentation it went through ...after a few clarifications here and there which we were able to sort out. The analysis is what now started delaying the process ...because of the ...because of the hiccup in the analysis ...but that was sorted out after a while and it was analysed. The results were found satisfactory and it was registered (Interview with KENREG1, 05/07/04).

There was a perception that the letter of the law was applied more strictly for local manufacturers (AM2) than was the case for large multinational companies who were given the benefit of the doubt (Interview with KENIND, 30/06/04). The case of AM2 also brought to the fore the disconnect between the national antimalarial drug policy and drug registration. The national antimalarial drug policy recommends the use of combination therapies (specifically, ART-LUM) and for this reason discourages registration and use of antimalarial monotherapies (Chapter 2). However, by law, manufacturers are only required to prove the safety, efficacy, and quality of their products (mostly in line with internationally recognised pharmacopoeia) and whether or not certain vertical programmes in the country adopt such products is considered to be outside the realm of registration. In

order for the local companies to 'profit' from national policy, they need to provide what the policy demands, failure of which results in exclusion:

> **KENIND:** Secondly, because it is a newer product, the drug registration and the malaria control programme policies don't seem...they don't synergise each other. Whereas AM2 is required [in the] pharmacopoeia, the monographs, Martindale's and so forth will give five to seven days treatment, the malaria control programme will want it to be used for three days in combination and they are discouraging use as a single molecule. In effect, when we want to fulfil drug registration requirements, you've got to go with what is pharmacopoeial; and that is a seven day treatment regime, which is now different from what the situation is locally. In which case, there is no adaptation. In as much as we would like to adapt to the local situation, we cannot do because the two institutions are not...they don't work...the are not harmonised (Interview with KENIND, 30/06/04).

> **KENREG1:** Now the need...the issue of people saying that the drug registration working with the National] Malaria [Control] Programme, I think there is still a lot of work required in terms of probably coordinating so that they can be able to know what is available within the country because ...it would be useful to know probably which other options, how many different options, but these are issues which even the companies are able to pick up because by the time they are putting in applications for registration they will have monitored what is selling out there and in terms of registration, we normally register based on documentation also and based on evidence. So the registration is normally not just for the purpose of registration, but there is also information that is provided to support the applications. Of course, the ones which have been registered, are the ones which have actually been able to prove that the drugs can actually work. There are so many others which have been registered...which have been rejected which probably could not be able to justify the reasons why they are putting forward the applications (Interview with KENREG1, 05/07/04).

Adding to this layer of policy disconnect is the inclusion of some artemisinin monotherapies like dihydroartemisinin in the latest edition of the KEDL (MoH, 2003), on which public sector procurement by KEMSA is largely based, although not legally binding (Section 3.3.1).

3.4 Discussion

Whilst this chapter was meant to be a descriptive one laying out the country drug regulatory context for Kenya, and not a substantive one designed to contribute to the literature on regulation of the health sector and that of the pharmaceutical sector, it does nonetheless suggest that Kenya is probably in the "paper" regulation phase of Soderlund & Tangcharoensathien (2000); the legislative framework for effective drug regulation exists on paper, but this is rarely enforced. Indeed, the WHO estimates that only 17% of member states have well-developed drug regulatory capacity, 50% show varying levels of development and operational capacity and the rest have no drug regulatory authority (DRA) or the DRAs capacity is weak (WHO, 1999). This means that even if there was political will to enforce drug-related regulations, the infrastructure in most countries is either lacking or wanting.

3.4.1 Criteria for drug registration

Traditionally, safety, quality, and efficacy are the criteria on which regulatory decisions are made (Videau, 2001; Waller, 2001). Although the cost of drugs is not a requirement at the point of registration in most countries (Videau, 2001), cost to the public sector is sometimes regulated, albeit indirectly. In developing countries like Kenya, this is done by way of the concept of essential drugs whose selection criteria involves cost as one of the considerations (MoH, 1994b), i.e. "a white list" of drugs to be used in a country is developed from registered alternatives. In developed countries like the UK, costs are contained by way of reimbursement schemes that place maximum allowable profits on drugs sold to the public sector (NAO, 2003), effectively "black-listing" products that will not be reimbursed by the health care system.

3.4.2 Drug registration process

The registration process entails scrutiny of evidence submitted to regulators by the licence applicant. A company that wants to register a product in any given country will typically prepare what is termed a dossier for evaluation by the country's drug regulatory authority (DRA). The dossier contains evidence as to the safety and efficacy of the drug's active pharmaceutical ingredient (API) from the clinical trial data and the quality of the finished product. The dossier will also contain information on all aspects of the pharmaceutical manufacturing process. The type and amount of information and the level of scrutiny differs, depending on whether the drug is a new chemical substance or a generic. Generic drugs are manufactured after the patent period has expired for the originator or innovator product. In most countries, for new chemical substances, primary safety and clinical efficacy data are required. For generic products, however, the requirements are less stringent. This is because the drug molecule has been in use for a long time (typically patent periods range from 17 to 20 years) and its safety and efficacy are arguably well established. Hence, it is sufficient to demonstrate bioequivalence[14] or pharmaceutical equivalence with the innovator or originator product.

3.4.3 Limitations of drug registration and need for post-marketing surveillance

Drug registration process in Kenya is largely perceived as working (for those drugs which pass through it) and it is generally agreed that this is probably the strongest element in the Kenyan regulatory regime (Interviews with KENREG1, 05/07/04; KENAC2, 07/07/04; KENREG2, 02/08/04). However, the drug registration process has an inherent limitation, and more so for Kenya where only half the products pass through registration. By the time a product is brought to market, only a few thousand people (about 2000) would have been

[14] "Pharmaceutical equivalents" are drug products that contain identical active ingredients and are identical in strength or concentration, dosage form, and route of administration. However, pharmaceutical equivalents do not necessarily contain the same inactive ingredients; various manufacturers' dosage forms may differ in colour, flavour, shape, and excipients. The terms "pharmaceutical equivalents" and "chemical equivalents" are often used interchangeably. "Bioequivalence" is a comparison of the bioavailability of two or more drug products. Thus, two products or formulations containing the same active ingredient are bioequivalent if their rates and extents of absorption are the same.

exposed to it by way of clinical trials. Secondly, drugs are tested on a very narrow group of patients, in a tightly controlled environment. Conversely, under routine use, patients excluded during the clinical trials (e.g. pregnant women and children) might well use the drug. Because of these limitations, regulators see the registration process as a means to ensure public health and not as an end in itself. Therefore, continuous monitoring of safety (by way of post-marketing surveillance) is needed in order to detect adverse drug events that can only be seen under mass use. There is no effective post-marketing surveillance system in Kenya for pharmaceuticals and the other domains of drug regulation (licensing and inspection of personnel, premises, etc) are also perceived to be ineffective (Interviews with KENAC1, 19/03/04; KENIND, 30/06/04; KENREG1, 05/07/04; KENAC2, 07/07/04; KENREG2, 02/08/04).

The consequences of a lack of post-marketing surveillance system in Kenya has been enormous. There are a substantial number of unregistered products in circulation and whose safety, quality and efficacy cannot therefore be guaranteed (Chapter 5). In terms of quality, manufacturers and importers of drugs typically present very good quality products at the time of registration, but market sub-standard products afterwards (Interviews with KENAC1, 19/03/04; KENREG1, 05/07/04; KENAC2, 07/07/04). In addition, drugs that have been withdrawn from developed country markets are in circulation in developing country markets like Kenya. In 1998 for instance, the NQCL analysed an AM drug that was submitted for registration and which was purporting to contain sulfalene (sulfamethopyrazine), but which instead contained sulfamethopyridazine, a closely related substance with the same physico-chemical properties, but which had been banned for human use almost a decade earlier and is now found only in veterinary products. Sulfamethopyridazine had been included in the WHO's 1991 *Consolidated List of Products Whose Consumption, and/or Sale Have Been Banned, Withdrawn, Severely*

Restricted or not Approved by Governments (WHO, 1991). On further investigation, it was noted that indeed at least seven other brands of SP containing sulfamethopyridazine were in circulation and as such NQCL recommended that they be withdrawn (Dr E Ogaja, personal communication). It is possible that some of these products are still in circulation given that a substantial number of products do not pass through the regulatory pipeline at all (see Chapter 5). Although it can be argued that the presence of such drugs might be because of a risk: benefit assessment that favours the retention of such products in the market (e.g. in the case of chloramphenicol), the fact that a drug like SP with many branded options that include banned substances in circulation points to a weak regulatory environment. Ineffective drug regulation in Kenya has been attributed variously to inadequate human and financial resources, inadequate or conflicting policy and legislative provisions and lack of political will (Interviews with KENAC1, 19/03/04; KENIND, 30/06/04; KENREG1, 05/07/04; KENAC2, 07/07/04; KENREG2, 02/08/04).

A key strategy that has hitherto remained unexplored in Kenya to redress these deficiencies in post-marketing surveillance is that of conditional licensing. Under such a scheme, if there are concerns about a product at the time of registration (for instance the safety of artemisinin-combination therapies like ART-LUM, Coartem®), the product(s) could be licensed subject to a pharmacovigilance system being set up by the applicant. Such a system would first transfer the burden of proof to the applicant and secondly it would circumvent passive reporting, which depends on a well functioning health care delivery system (which is lacking in Kenya). This would save money for resource-constrained developing country drug regulatory authorities in the short term and save lives in the end. Regardless of the strategies adopted, there is clearly a need to strengthen post-marketing surveillance system and enforcement of best practices (e.g. GMP) in Kenya to ensure the continued safety, efficacy, and quality of antimalarial drugs post-registration.

3.4.4 Implications of the Kenyan regulatory environment for ART-LUM, the new first-line antimalarial policy

The ambiguities and weaknesses of the Kenyan regulatory system are brought into sharp focus by the current antimalarial drug policy change from SP to ART-LUM (see Chapter 2 for the evidence leading to this decision). Apart from the financial hurdle in its way, ART-LUM faces a number of regulatory hurdles that need to be addressed if it is to be accessible to all Kenyans. There is only one fixed-dose, co-formulated ART-LUM available on the market, i.e. Coartem®, manufactured by Novartis Pharma AG. Coartem® has been offered to the WHO at a concessionary price of USD 0.90 and 2.40 per child and adult doses, respectively and this deal is intended only for the benefit of the not-for-profit public sector facilities (WHO, 2003c). Countries requiring ART-LUM send their orders to WHO which procures on their behalf from Novartis. Some stakeholders in Kenya have queried the legality of this pooled procurement system since government tenders are usually awarded on a competitive basis and therefore term this arrangement 'anticompetitive'. Such critics argue from the point of view that there are other artemisinin-based combination therapies (ACTs) on the market and that the government need not restrict itself to Coartem® (PSK, 2004) Whereas such accusations are largely without scientific merit (because the other available ACTs are unsuitable for Kenya (AS-MEF) or are contrary to WHO policy (AQ-AS, AQ-SP), leaving only ART-LUM), they have nonetheless resulted in a hostile environment for Coartem® and a delay in its roll-out (Chapter 2).

The debate on Coartem® has also brought to the fore the inconsistency of certain elements within the KNDP. Walley and colleagues (2000) argue that for a National Drug or Pharmaceutical Policy to work successfully, 'each element should be complementary to all other elements, or at least neutral'. The National Malaria Control Programme (NMCP) advocates the use of ACTs (specifically Coartem®) and discourages the use of artemisinin

monotherapies because of the risk of selecting resistant parasites. Therefore, the presence of these products in the market is seen as a threat to the national antimalarial drug policy (MoH, 2004b). The paradox is that by law, an arm of the KNDP-drug registration-is only allowed to look at the safety, quality, and efficacy of drugs seeking market approval (GoK, 1989). The PPB contends that artemisinin monotherapies in the market have proved their safety, quality and efficacy and there is therefore no legal basis on which not to register them or to deregister existing ones if need be (Interview with KENREG1, 05/07/04). Adding to this conundrum is the inclusion of artemisinin monotherapies like dihydroartemisinin in the KEDL, on which public sector drug procurement is largely based (MoH, 2003). Further, Coartem® is not included in the KEDL (MoH, 2004b). There is clearly a need to coordinate elements of the KNDP to ensure a coherent and mutually supportive policy framework for Coartem® in Kenya.

Coartem® was initially registered in Kenya as a four-dose regimen for the private sector and could only be obtained from pharmacies (Pharmacy Only medicine). Subsequent studies showed that a six-dose regimen was more efficacious and this is what has been registered for provision through the public sector through the WHO-Novartis agreement (Prof R Snow, personal communication). Two issues need to be addressed in this public-private dichotomy. First is how the four-dose regimen already in circulation in the private sector and that of failed drugs such as SP will be mopped up in an environment where there is no effective recall mechanism for drugs. Second, the exclusion of the private-for-profit sector in the WHO-Novartis agreement also means that there is an incentive for leakage of the product from the private sector to the public sector where it will fetch higher profits than the commercially available one. Although 'public Coartem®' and 'private Coartem®' have different packaging (see Figures 3.4 and 3.5), this has not stopped products marked GoK from being sold in the private sector in the past. One of the

proposed strategies to minimise this is the introduction of price controls in the private sector to a maximum of USD 2.40 per adult dose and USD 0.90 per child dose i.e. similar to what it would cost the government. The legality of such a measure in an environment of economic liberalisation remains to be seen and there are no obvious precedents for this.

Figure 3.4: Public sector Coartem®

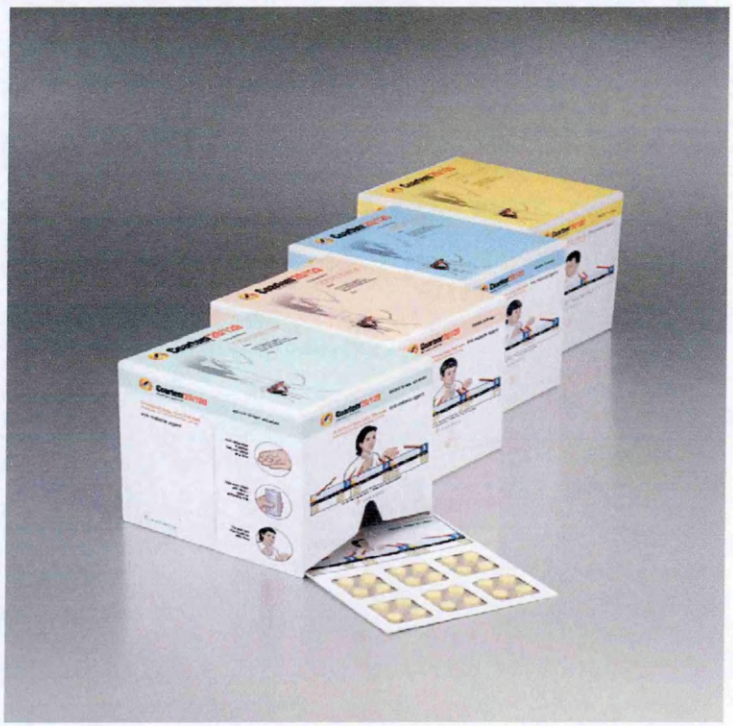


Figure 3.5: Private sector Coartem®

3.5 Summary

Drugs in Kenya are regulated by the PPB. The PPB licenses drug outlets, manufacturers, and distributors (channels); registers pharmacists and pharmaceutical technologists (personnel); and registers new products for the market. The PPB is also mandated to ensure drugs are safe, efficacious and of high standard of quality post-registration by way of post-market surveillance (enforcement).

Interviews and documentary evidence revealed a number of shortcomings of the present framework. A substantial number of antimalarial drugs in Kenya do not pass through the registration pipeline (Chapter 5). Such drugs can only be detected through a functional post-marketing surveillance system. There is no functional post-marketing surveillance system in Kenya and this poses a logistical challenge to moping up failing antimalarial drugs like SP and generally unregistered and unsafe drugs in the market. For a national drug or pharmaceutical policy to work, each element should be complementary to all the other elements or at least neutral. There is a clear disconnect between some elements of the KNDIP such as drug registration and the objectives of some vertical programmes such as the National Malaria Control Programme's antimalarial drug policy. There is need to harmonise elements of the KNDIP to make sure that none of the components undermines malaria control in Kenya.

Drug regulation in developing countries like Kenya is a challenging task and more needs to be invested to ensure the safety, quality and efficacy of drugs not only at the time of registration, but post-registration. The introduction of new single-source ACTs for malaria case-management present particular and new challenges to already fragile systems.

CHAPTER 4:

Fever management practices and drug use among households in sentinel districts

4.1 Introduction

The basic premise that appropriate case-management will result in demonstrable gains in child survival depends critically upon whether the right drug (safe, efficacious and of acceptable quality) is administered at the correct dose as early as possible in the disease event and that treatment courses are completed (Goodman *et al.*, 2001). African heads of State met in Abuja in April 2000 and agreed, as part of the Roll Back Malaria (RBM) initiative, to ensure that at least 60% of all fevers would be managed in this way by the year 2010 (WHO, 2000c). This objective is in line with the Kenya National Malaria Strategy (KNMS) described previously in Section 2.4.2. Chapter 2 provided the context of drug use and its role within the KNMS and the broader health sector, whilst Chapter 3 described the structure and weaknesses of the legislative and regulatory framework for drugs in the formal health sector and the private sector. This chapter focuses on the sources, costs, timing, and types of treatment for fevers among children under five years of age in the four study districts. In addition, the extent to which current paediatric fever management falls short of anticipated targets set by the Kenyan government will be examined.

4.2 Materials and methods

4.2.1 Study sites

Snow *et al.* (1998) divided Kenya into areas of low, moderate, high, and unstable malaria endemicity (Section 2.3). The model has been simplified by the National Malaria Control Programme for planning and management of disease control with the country being divided into the following four areas (http://www.kmis.org, accessed 30/07/04):

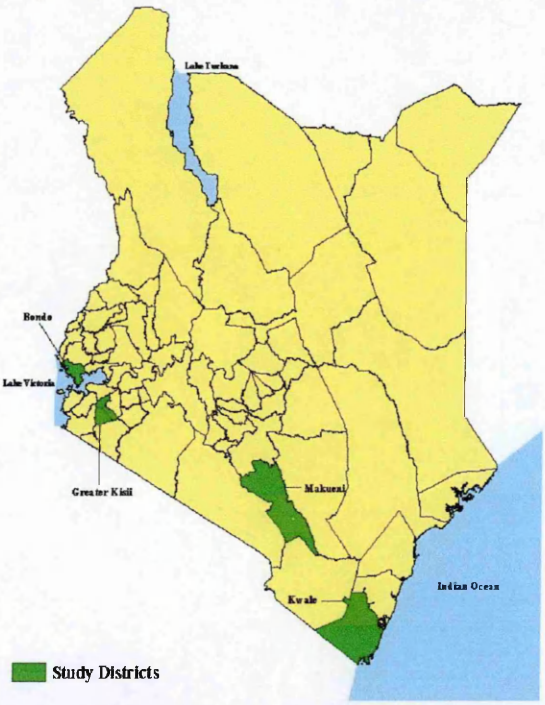
1. Endemic areas: transmission common every year, immunity acquired by the community before adulthood and risks of disease and death from malaria are concentrated amongst children below five years and pregnant women.

2. Highland, epidemic-prone areas: on an average year there is potential for limited transmission and therefore low risk of malaria, but variations in rainfall and ambient temperatures between years can lead to epidemics which may occur every three to five years.

3. Arid, epidemic prone-areas: unable to support the breeding of malaria vectors except around either man-made water bodies or perennial rivers. Consequently, malaria infection risks are extremely low, locally acquired clinical disease is rare and the population do not develop immunity. However, unusual rainfall and flooding can lead to severe epidemic crisis conditions which although rare can lead to devastating levels of disease and death among the entire population.

4. Low risk areas: these represent areas with exceptionally low risk of acquiring malaria infection.

Figure 4.1: Map of Kenya showing the study districts



Four districts were purposively sampled for this thesis in collaboration with the DOMC so that they may coincidentally form part of a baseline for monitoring progress towards targets set in the KNMS. The four districts were sampled to represent the various *P. falciparum* ecological settings in Kenya and reflect the diverse population and climatic conditions across the country and coincident with DOMC districts used to monitor antimalarial drug sensitivity (Figure 4.1). Greater Kisii district was selected to represent an area of "highland" transmission; Kwale: seasonal, intense transmission; Bondo: perennial, intense transmission and Makueni; semi-arid, acute seasonal transmission. A detailed description of each of the districts and their basic demographic, health, literacy, and malariometric indicators follows.

4.2.1.1 Greater Kisii

Greater Kisii, which covers a land area of 1,310 km^2, comprises Kisii Central and Gucha districts and is one of the twelve districts that make up Nyanza province of Kenya. The district is in the western highlands at an altitude between 1400 to 2200 metres above sea level. The district lies between latitude 0.500° and 0.967°S and longitude 34.700° and 35.083°E. The Abagusii, who are the main ethnic group in the district, are an agricultural community and grow both cash crops like tea, coffee and pyrethrum and subsistence crops like maize, beans, finger millet, potatoes, bananas and groundnuts for home consumption. The total population of the district during the 1999 national census was 952,725 people with a population density of 706 persons per square kilometre and children under five comprising 15.6% of the population (CBS, 2001a). The climate is highland equatorial and average annual rainfall is well above 1500 mm per annum. There are two main rainy seasons; the long rains, which occur from March to June, and the short rains from September to November. The 1999 national census revealed that 31.4% of Abagusii males (15 to 54 years of age) and 25.9% of Abagusii females remained economically inactive. The typical Abagusii house is made of mud and has an iron roof (CBS, 2001c). A 1994 Central Bureau of Statistics (CBS) survey among 261 Abagusii children aged 6 to 60 months showed that 40.6% of the children were stunted, 23.4% undernourished and 6.2% wasted (CBS, 1994).

4.2.1.2 Kwale

Kwale district covers a land area of 8,335 km^2. The district is in Coast province of Kenya, near the border with Tanzania. Kwale is adjacent to the Indian Ocean on the southeast of the country and lies at an altitude range of 0 to 650 metres above sea level. The district lies between latitude 3.550° and 4.667°S and longitude 38.450° and 39.667°E (CBS, 2001a). The Mijikenda, who are the main ethnic group in the district, comprise nine sub-groups,

two (Wadigo and Waduruma) of which form the main inhabitants of Kwale with the other groups settling in other adjacent districts of Coast province (Mwangudzu, 1983). The main economic activity of the Mijikenda is agriculture with crop income accounting for almost a third of monthly household income in Kwale. The most commonly cultivated crops are maize, coconut, and cashew nuts. Tourism is also a major economic activity, the main attractions being wildlife, historical sites, and other coastal features. During the 1999 national population census, the total population of Kwale district was 952,725 with a population density of only 60 persons per square kilometre, a tenth that of Greater Kisii district. Children under five comprised 17.3% of the population of Kwale (CBS, 2001a). The climate is described as monsoon, hot and dry from January to April while June to August is the coolest period of the year. The annual average rainfall varies from 900 to 1500 mm per annum along the coastal strip and 500 to 600 mm further inland. There are two rainy seasons; the long rains, which occur from March to July, and the short rains from November to December. The 1999 national census revealed that 17.7% of the male residents of Kwale (15 to 54 years of age) and 29.9% of females remained economically inactive (CBS, 2001c). A 1994 CBS survey showed the prevalence of stunting, under-nutrition and wasting among children in Kwale aged 6 to 60 months to be 53%, 29.1% and 5.2% , respectively (CBS, 1994).

4.2.1.3 Bondo

Like Greater Kisii, Bondo district is in Nyanza province of Kenya. The district lies between latitudes 0.400°S and 0.050°N and longitude 33.967° to 34.433°E and covers a land area of just 987 km^2. The district is adjacent to Lake Victoria, a large fresh water lake in western Kenya shared between Kenya, Uganda and Tanzania (CBS, 2001a). The Luo are the main ethnic group in the district accounting for 95% of the population. Polygamy is common among the Luo with different wives living with their children in different houses

within a single-family compound (Cohen & Odhiambo, 1989). The Luo are mainly subsistence farmers and grow maize, sorghum, beans, cassava, finger millet, and sweet potatoes. Cash crops include cotton and sugar cane. In 1999, the district had a population of 238,780 people with a population density of 240 persons per square kilometre and children under five comprising 16.9% of the population (CBS, 2001a). There are two rainy seasons in Bondo: the long rains which occur between March to June and the short rains between August and November. The district is drier to the south along the shores of Lake Victoria, but wet towards the hinterland with increasing altitude. In 1999, 26.9% of males aged 15 to 54 in Bondo were economically inactive. Likewise 30.9% of their female counterparts were economically inactive (CBS, 2001c). In a 1994 CBS survey among 138 children aged 6 to 60 months, the prevalence of stunting, under-nutrition and wasting was 33.8%, 15.8% and 3.8% , respectively (CBS, 1994).

4.2.1.4 Makueni

Makueni district is situated in Eastern province of Kenya. The district lies between latitudes 1.523° and 2.987°S and longitudes 37.144° and 38.517°E and covers a land area of 8,226 km^2. In 1999, the district's population stood at 771,545 persons and there were 93.8 persons per square kilometre, although this varied with the northern wetter areas being more densely populated than the southern dry areas. Children under five years of age accounted for approximately 14% of the total population (CBS, 2001a). Rainfall is limited and seasonal averaging 800 mm to 1200 mm per year in the cool and wet hilly areas to the north and central parts of the district, and 200 mm to 900 mm in the hot and dry low-lying areas. The district is mainly inhabited by the WaKamba (97% of the population) who live in compounds consisting of 2 to 4 huts and a food store. The WaKamba grow maize, beans, pigeon peas, and cowpeas for subsistence and coffee and cotton for cash. In the 1999 census, 27.3% of males aged 15 to 54 years in Makueni were economically inactive.

Likewise 39.5% of their female counterparts were economically inactive (CBS, 2001a). The prevalence of stunting, wasting, and under-nutrition among 148 children aged 6-60 months was undertaken by the CBS in Makueni district in 1994: 50% of children were stunted, 22.3% under-nourished and 2.7% wasted (CBS, 1994).

4.2.2 Basic district level indicators

Table 4.1 shows some important demographic, poverty, literacy and health service indicators for the four study districts. Greater Kisii was the most densely populated of the four districts, followed by Bondo, Makueni, and Kwale, respectively. The populations in the districts essentially live in rural areas with over 80% of households in all districts found in rural enumeration areas (EAs). In Kwale, an EA had, on average, 604 people, in Greater Kisii 482, in Makueni 437 and Bondo 355 people in 1999. Greater Kisii had the largest number of households with 190,091 followed by Makueni 144,320, Kwale 92,594, and Bondo 56,607.

The 1999 population figures were projected to 2002 so that population data used in the analysis was that of the year when most of the surveys presented in later chapters were conducted. The projected population for 2002 for Bondo was 242,098, Greater Kisii 965,963, Kwale 505,447 and Makueni 781,327. The ratio of health facilities, personnel, beds, and retail outlets were computed using the 2002 projected population (Table 4.1). The number of people per health facility using the 2002 population showed that overall; there were fewer people per health facility in Makueni (1:3,887) followed, in order of decreasing coverage, by Bondo (1:4,567), Kwale (1:5,157) and Greater Kisii (1:5,221). The ratios of clinical health workers to population showed that in Greater Kisii, there was 1 health worker for every 1,177 people, followed in order of decreasing coverage by Kwale 1:1,300, Makueni 1:1,760 and Bondo 1:2,070. The coverage of inpatient beds was the

highest in Greater Kisii with 1 hospital or health centre bed for every 480 people. This was followed by Bondo with 1:760, Kwale 1: 1,000 and Makueni 1:1,100. The ratio of retail outlets to population was 1:482 in Greater Kisii, 1:598 in Bondo, 1:756 in Makueni and 1:888 in Kwale.

The most recent poverty report derived from a household survey conducted in 1997 by the CBS showed that 57% of people in Greater Kisii lived below the poverty line (living on less than KES 1,239 per adult per month in 1997 or 19.6 USD). The district was ranked the 17th poorest district in Kenya. In Kwale, 61% of people lived below the poverty line in 1997. The district was ranked the 14th poorest in Kenya. Bondo was ranked 15th poorest district in Kenya and 58% of people in Siaya district, of which Bondo was part during the survey, lived below the poverty line. With 74% households classified as living below the poverty line, Makueni ranked second poorest in the country after Homa Bay district in Nyanza Province (CBS, 2000a). This finding has been backed up by a more recent survey which found that about 70% of households in Makueni were living in poverty (Nantulya *et al.*, 2001).

Among poor adults aged 15 years and above, the lowest literacy rates in the four districts were recorded in Kwale with only 46% of poor people able to read or write a short, simple sentence. Literacy rates among the poor in the other districts were 78%, 63% and 75%, for Greater Kisii, Bondo, and Makueni, respectively. Among the non-poor, the lowest literacy rates were recorded in Bondo with 62% of those surveyed able to read and write. Literacy rates among the non-poor in the other districts were 84% for Greater Kisii, 65% for Kwale and 79% for Makueni (CBS, 2000b).

Table 4.1: Demographic, poverty, literacy, and health service indicators for the four study districts.

Indicator	Greater Kisii	Kwale	Bondo	Makueni
Demographic				
Area (km^2)	1,310	8,295	960	8,266
Total population for 1999 (% rural)	952,725 (94)	496,133 (89)	238,780 (92)	771,545 (97)
Annual population growth rate (%)	0.0046	0.0062	0.0046	0.0042
Projected* population for 2002	965,963	505,447	242,098	781,327
Population density for 2002 (people per km^2)	737	61	252	95
Number of EAs 1999 (% rural)	1,975 (94)	822 (80)	673 (95)	1,766 (95)
Number of households 1999 (% rural)	190,091 (86)	92,594 (84)	56,607 (93)	144,320 (94)
Average number of people per EA (1999)	482	604	355	437
Poverty and Literacy indices				
Percent living below poverty line† (district poverty ranking)	57% (17)	61% (14)	58% (15)	74% (2)
Literacy rates‡ among poor adults >= 15 years	78%	46%	63%	75%
Literacy rates among non-poor adults >=15 years	84%	65%	62%	79%
Health facilities and personnel				
MoH	44	50	21	59
Mission/NGO	23	10	10	29
Private	118	38	22	113
Total number of facilities	185	98	53	201
Retail outlets	2,002	569	405	1,034
Doctors	61	14	8	25
Clinical Officers	84	50	19	53
Laboratory technologists/technicians	123	56	24	41
Nurses	553	269	66	325
Total health personnel	821	389	117	444
Health service indices				
Health facility: population	1: 5,221	1: 5,157	1: 4,567	1: 3,887
Retail outlets: population	1: 482	1: 888	1: 598	1: 756
Doctors: population	1: 15,835	1; 36,103	1: 30,262	1: 31,253
Clinical Officers: population	1: 11,500	1: 10,110	1: 12,742	1: 14,742
Laboratory technologists/technicians: population	1: 7,853	1: 9,025	1: 10,087	1: 19,057
Nurses: population	1: 1,747	1: 1,880	1: 3,668	1: 2,404
Total health personnel: population	1: 1,177	1; 1,300	1: 2,070	1: 1,760
Beds: population	1: 480	1: 1,000	1: 761	1: 1,100

* The equation $P_{1999}=P_{2002}\, e^{rt}$ was used in the projection of population, where P_{1999} was the 1999 population census and P_{2002} was the required 2002 population, t was the number of years between 1999 and 2002 and r was the average annual growth rate (Deichmann, 1996).

† Overall poverty line-urban and rural households living on less than KES 1,239 per adult per month in 1997 (CBS, 2000a).

‡ Literacy defined as ability to read and write a short, simple statement (CBS, 2000b).

Table 4.2 shows selected malariometric data for the four districts based on data abstracted from the MARA/ARMA collaborative programme, involving a comprehensive review of all published and unpublished data on prevalence of malaria infection in childhood and malaria vectors in the sub-region (Omumbo & Snow, 2004). Data showed that *Plasmodium falciparum* prevalence rates among children aged 0 to 10 years varied between the districts with Greater Kisii (low transmission) and Makueni (semi-arid, acute seasonal transmission) having the lowest prevalence (17 and 16%, respectively). Bondo with intense, perennial transmission and Kwale with seasonal intense transmission had similar *P. falciparum* prevalence rates in this age group. Among school-going children, the trend in *P. falciparum* prevalence was similar, although Kwale showed a similar prevalence to Greater Kisii (32% and 31% , respectively). *Anopheles gambiae* and *An. funestus* were the principal vectors in Greater Kisii, Kwale, and Bondo; information on the types of vectors was not available for Makueni. These community-based parasitological surveys suggest that Greater Kisii and Makueni are best described as hypo-mesoendemic, Kwale as hyper-endemic and Bondo as hyper-holoendemic [15].

[15] Hypoendemicity-parasite rates not exceeding 10% in children aged 2-9 years, but may be higher for part of the year. Mesoendemicity-parasite rates between 11-50% in the same age group. Hyperendemicity-parasite rates constantly over 50% in the same age group. Holoendemicity-parasite rates constantly over 75% among infants aged 0-11 months (Metselaar & Van Theil, 1959).

Table 4.2: Selected malariometric data for the four study districts derived from a variety of sources (Omumbo *et al.*, 1998; 2004; DOMC, 2001b-e; http://www.eanmat.org, accessed 11/08/04).

Indicator	Greater Kisii	Kwale	Bondo	Makueni
Combined *P. falciparum* parasite rate* from community surveys among children aged 0-10 years (Kenya MARA/ARMA database)	17% (n=1783)	55% (n=369)	58% (n=1964)	16% (n=811)
Combined *P. falciparum* rates among school children aged (5-15 years) (Kenya MARA/ARMA database)	31% (n=1597)	32% (n=1565)	57% (n=508)	11% (n=1142)
Principal vectors in the district (Kenya MARA/ARMA database)	*Anopheles gambiae s.l* *An. funestus*	*An. gambiae s.s* *An. arabiensis* *An. funestus* *An. merus*	*An. gambiae s.s* *An. arabiensis* *An. funestus*	n.a†
Malaria outpatient diagnoses (OPD)‡ Malaria OPD among children < 15 years Malaria OPD among adults	 49.8% 50.2%	 54.3% 45.7%	 57.6% 42.4%	 55.0% 45.0%
P. falciparum slide positivity rate among presumed malaria outpatient and inpatient cases (DOMC 2001a; 2001c; 2001d; 2001d)	67%	27%	71%	22%
Malaria inpatient admissions (as % of total admissions) Children < 15 years Adults	 55% 46%	 51% 19%	 34% 20%	 48% 17%
Percent death attributable to malaria Children < 15 years Adults	 24% 26%	 36% 15%	 26% 20%	 23% 16%
Hospitalised malaria case-fatality rates§ Children < 15 years Adults	 4.8% 5.1%	 4.2% 7.3%	 6.7% 9.0%	 7.5% 12.3%
Clinical efficacy of SP and AQ in 2003 Day 14 ACPR for SP Day 14 ACPR for AQ Day 28 ACPR SP Day 28 ACPR for AQ	 70.4% 94.7% 39.6% 77.0%	 86.8% 100.0% n.a n.a	 62.5% 98.2% 30.9% 83.0%	 83.1% 88.4% 46.4% 68.5%

* Parasite rate-prevalence of peripheral blood-stage infections among a community, usually collected through random, community-based samples (Snow & Gilles, 2002).
† n.a-not available
‡ Malaria OPD-proportion of all malaria diagnoses that were recorded among outpatients.
§ Malaria case fatality rate implies the ratio of the number of deaths from malaria to the number of cases of malaria admitted to hospital.

In 2001, the DOMC reviewed outpatient and in-patient health facility records of government facilities (GoK) in the districts in collaboration with the DHMTs (DOMC, 2001b; 2001c; 2001d; 2001e). From these surveys, it can be deduced that malaria is a common occurrence in the districts accounting for between 42 and 50% of outpatients among adults and between 50 and 58% among children less than 15 years (Table 4.2). Among children less than 15 years, malaria also accounted for 34 to 55% of all inpatient admissions and between 23 and 36% of all-cause mortality in hospital. Likewise, for adults, the disease accounted for 19 to 46% of all hospital admissions and 15 to 26% of all-cause mortality in hospital. Overall, case-fatality rates for hospitalised malaria patients ranged from 4.2 to 12.3% in the districts.

Figures 4.2 to 4.5 show paediatric (< 15 years) malaria admissions in the district hospitals of the four districts plotted against monthly rainfall from 1998 to 2000. The acute seasonal nature of clinical malaria in Greater Kisii is evident from Figure 4.2 with the peaks in paediatric malaria admission coinciding with the long rains and demonstrating marked between-year variation; so is the seasonal nature of clinical malaria in Kwale with the peaks in paediatric malaria admission coinciding with the long and short rains (Figure 4.3). There is lack of any marked seasonal pattern of clinical malaria in Bondo despite small peaks in paediatric malaria admission coinciding with the long and short rains (Figure 4.4). The acute seasonal nature of clinical malaria in Makueni is evident from Figure 4.5 with the peaks in paediatric malaria admission coinciding with the long rains (DOMC, 2001b; 2001c; 2001d; 2001e).

Figure 4.2: Monthly malaria paediatric admissions among children < 15 years to Kisii District General Hospital (red) between 1998 and 2000 against rainfall in mm (blue).

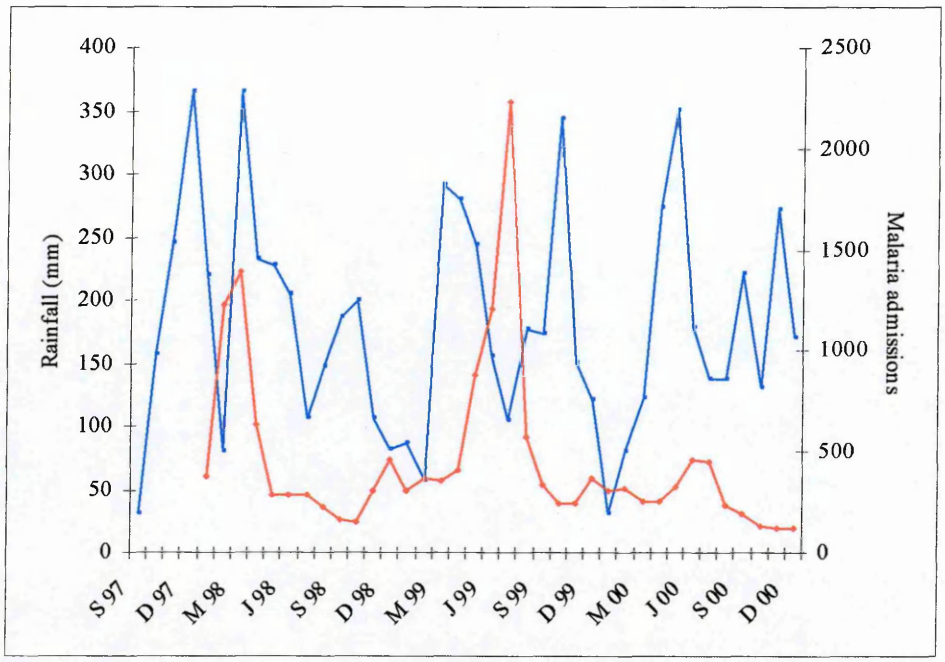


Figure 4.3: Monthly malaria paediatric admissions among children < 15 years to Msambweni District General Hospital, Kwale (red) between 1998 and 2000 against rainfall in mm (blue).

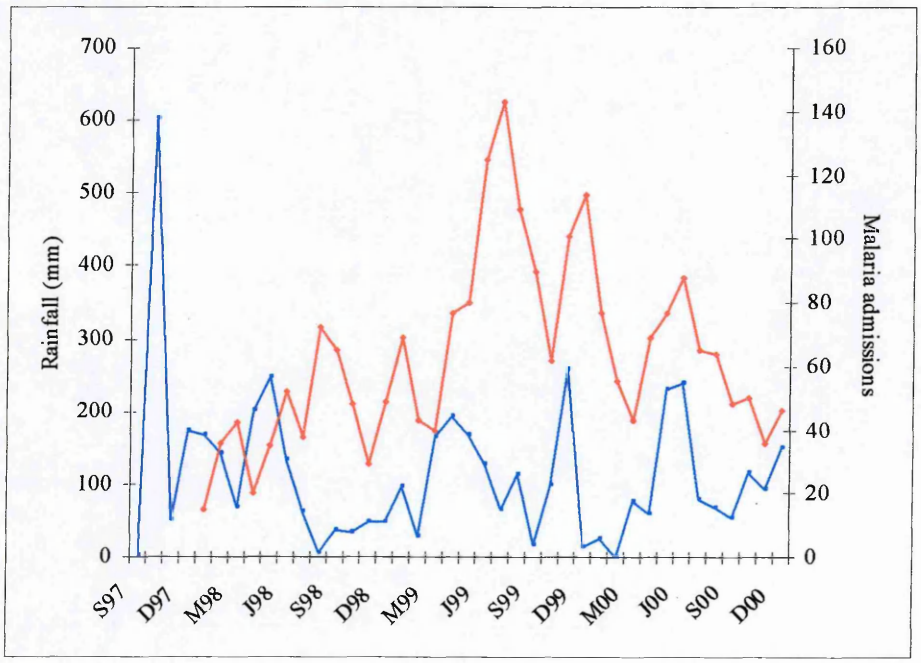


Figure 4.4: Monthly malaria paediatric admissions among children < 15 years to Bondo District General Hospital (red) between 1998 and 2000 against rainfall in mm (blue).

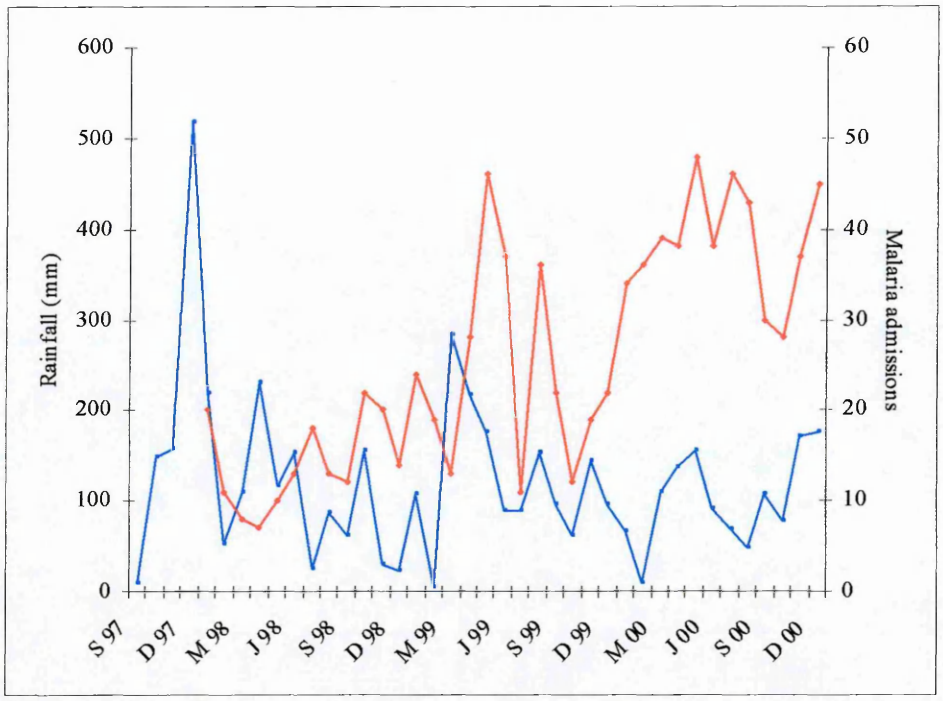
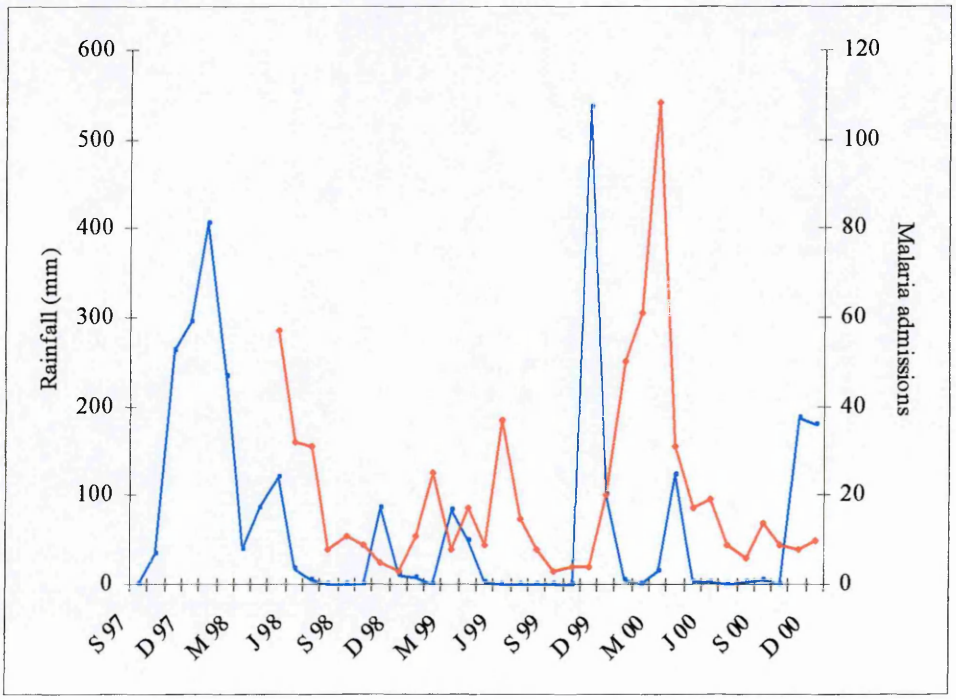


Figure 4.5: Monthly malaria paediatric admissions among children < 15 years to Makueni District General Hospital (red) between 1998 and 2000 against rainfall in mm (blue).



From the EANMAT database, the latest drug sensitivity studies (2003 for the other districts, and 2001 for Kwale) suggest that adequate clinical and parasitological response (ACPR) on Day 14 for SP was below 75% (change phase, see Chapter 1) for Greater Kisii and Bondo and above 75% for Kwale and Makueni (Table 4.2). However, ACPR on Day 28 was less than 50% in the study districts where follow up was done for 28 days. For AQ, ACPR on Day 14 was above 75% for all study districts. However, ACPR on Day 28 was below 75% for Makueni and marginally above 75% (77%) for Greater Kisii. Data were not available for Kwale district (Table 4.2. See Chapter 2 for more details on clinical efficacy of SP and AQ in Kenya).

4.2.3 The community survey: sampling approaches and study design

Maps of EAs, created by the CBS during the 1999 national census and representing approximately 1,000 people or 100 homesteads, were digitised and displayed within a Geographic Information System (GIS) platform (MAPINFO, Version 6.0, 1985-2000, New York, USA). Details of the development of the district-level GIS maps are presented elsewhere (Noor *et al.*, 2003). The GIS platform was used to construct a sampling frame of EAs to serve as the primary sampling units in each district. In the last national census (1999), an EA was defined by the CBS as an area representing between 500 and 1000 people or 100 homesteads and which can be covered by a single enumerator or census officer during the census night. EAs were classified as urban or rural based on a mixture of population size, infrastructure and expert judgment (CBS, 2001a; Noor *et al.*, 2003).

In each district, a population of 25,000 people was targeted for the community survey representing approximately 2,500 homesteads. This sample was selected to provide adequate power to define under-five mortality from retrospective reports of mortality events in each homestead during the preceding 12 months. Further, sampling of EAs was done to represent each district's settlement pattern with urban and rural EAs being sampled

until the target population in each strata was attained for each district. Table 4.3 shows the numbers of urban and rural EAs in the initial sampling frame for the four study districts, their respective population counts and the eventual numbers of EAs sampled for the community survey. Figure 4.6 shows the spatial distribution of sampled EAs in each of the districts. High-resolution road, topographical and landmark maps were generated for each sampled EA to assist in fieldwork.

Table 4.3: Sampling frame for the 2001 community survey in four districts of Kenya. Figures in parentheses represent the equivalent 1999 population.

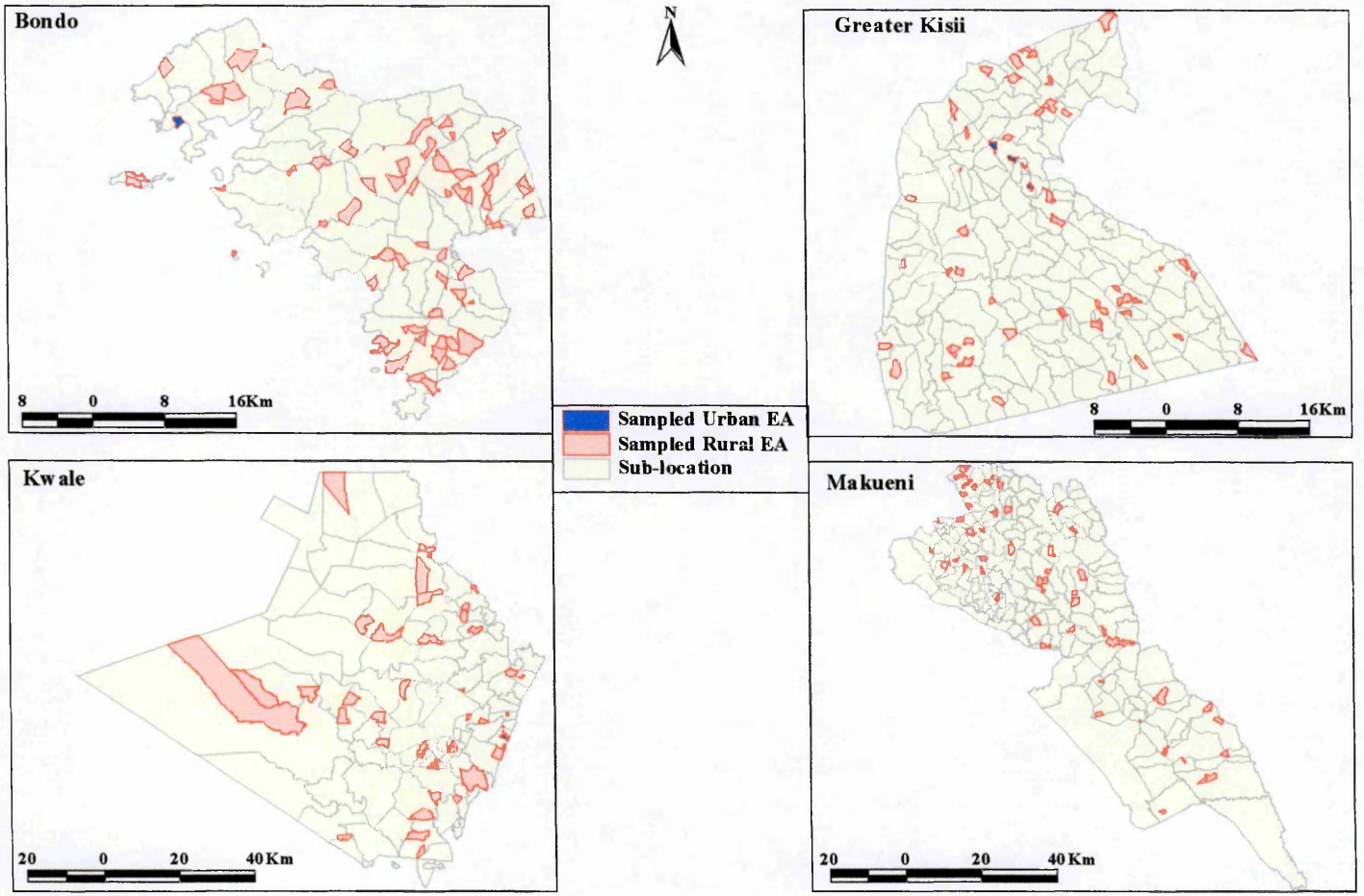
	Greater Kisii	Kwale	Bondo	Makueni
Number of EAs	673 (952, 725)	1,975 (496,133)	822 (238,780)	1,766 (771,545)
Number of urban EAs	36 (57,164)	118 (54,575)	164 (19,102)	95 (23,146)
Number of sampled EAs	66 (25,244)	54 (25,040)	48 (25,463)	62 (25,928)
Number of urban EAs sampled	3 (1,591)	6 (1,982)	12 (2,770)	5 (904)

4.2.4 Survey procedures

In each district, a local survey team of about 45 people with at least 12 years basic education was recruited. Staff were fluent in English, Kiswahili (the national language) and the local vernacular of each district and were trained over three days in the survey instruments, how to approach households and check data in the field and how to obtain informed consent for interviews. Field supervisors were recruited to oversee each district's survey work. Team leaders checked all data, completeness of homestead coverage, and technical details on a daily basis. Further on-going checks were performed at district and central levels to allow rapid clarification of issues arising.

Questionnaires (Appendix II) were translated into the local languages: KiKisii (Greater Kisii), KiKamba (Makueni), KiLuo (Bondo) and Kiswahili (Kwale) and piloted in each district to identify ambiguities in translation and inconsistencies in question interpretation according to local vernacular. Once in the districts, interviews were conducted within all homesteads of each sampled EA using the standard questionnaire. Interviews were conducted in Greater Kisii from December 2nd to 21st 2001, in Kwale from November 30th 2001 to January 26th 2002, in Bondo from December 5th 2001 to January 26th 2002 and in Makueni from November 30th 2001 to January 31st 2002.

Figure 4.6: A map of sub-locations showing the sampled enumeration areas (EAs) in the four study districts used during the community survey



Verbal consent was obtained from the head of the homestead for the interview to proceed. Homesteads were given unique codes and data collected included basic demographic data; information on exposure to indoor residual house-spraying and public awareness campaigns on malaria control; use of insecticide-treated nets, use of malaria curative and preventative strategies amongst pregnant women, the homestead's longitude and latitude using hand-held global positioning units; and treatment seeking behaviour for recent fevers in children under five years of age.

Reported fever was used as an entry point as this forms the prompt for malaria case-management guidelines by formal health service providers across Africa especially through the proposed Integrated Management of Childhood Illness (IMCI) (Gove, 1997). Furthermore, many communities in Kenya are unable to distinguish malaria-specific paroxysms from generalised fever and it is the latter that serve as the treatment action prompts (Section 2.5). More precise biological definitions of clinical malaria, involving elevated body temperatures and parasitology, are unable to establish treatment practices among morbid events that have resolved and for which "normal practice" can be defined.

At the homestead level, one child was selected randomly from the resident under five-year age group. This was done by putting the names of all children under five on pieces of paper, putting these in a hat or bag and asking the homestead head to select one child for interview. If the selected child was absent from the household then one further selection was made. Mothers or caretakers of the child were asked whether s/he had had a fever during the preceding 14 days and whether the child had a fever since the morning of the interview. Further enquiries were made to establish the duration of illness and the actions taken in response to illness recognition over the preceding 14 days. This approach to defining fever period prevalence and "appropriate" actions currently forms the basis of the RBM monitoring and evaluation tools within national demographic and health surveys run

by the MEASURE programme; (WHO & UNICEF, 2003). A two-week recall period is generally deemed optimum for morbidity surveys (Kroeger, 1985). In a study in an urban area of neighbouring Ethiopia comparing daily morbidity interviews with fortnightly interviews, Freij and Wall found that recent illness was overestimated and earlier events more easily forgotten, so that in a two-week recall period over- and under-reporting largely cancelled each other out (*op cit* Kroeger, 1983).

All actions involving the use of western-style medicines were investigated further using photo-illustrated drug charts of common proprietary antimalarial (AM) and antipyretic (AP) drugs available in the retail sector (Figure 4.7 for example). In addition, any health cards or medical notes were examined to record the drugs prescribed. The name of the providers and the time and costs of each action were also recorded.

Figure 4.7: An example of a product contained in the photo-illustrated visual aid used in the community survey.

4.2.5 Data quality assurance, analysis, and statistical approaches

Apart from range and consistency checks in the field in each district by project supervisors, at least 10% of interviews in each district were redone by supervisors to ensure reproducibility of responses. Complete re-interviews are generally not feasible nor recommended since motivating respondents to give second interviews is both difficult and maybe counterproductive in the long run (Kroeger, 1985). In all cases, there was concordance between first and second interviews, which supported the accuracy of reporting, and thus the reliability of survey data. In addition, in 10% of interviews, field teams were accompanied by supervisors to gauge their skill and performance; no issues were identified among any of the survey teams in the study districts.

All data were entered twice using MS-Access 2000 developed data-entry screens. The data entered by two independent clerks were verified for errors and corrected from the original proformas. Data were then subjected to a series of range and consistency checks to identify unlikely, outlying responses. These were re-checked with proformas, field supervisors, and a decision made on whether transcription errors had been made at the point of interview or whether the entries were to be deleted.

Analysis of frequencies was undertaken using combinations of Epi-Info Version 6.04d (Centers for Disease Control, USA), MS-Excel 2000, MS-Access 2000 (Microsoft Corp., Redmond, USA), and SPSS version 9.0 for Windows (SPSS Inc., Chicago, USA). Non-parametric Kruskal Wallis test was used to compare medians and chi-square tests (Pearson's χ^2) used to compare proportions. When comparing many groups, such tests only point out that at least one group is different from at least one other, thus necessitating post-hoc multiple comparisons (like the Bonferroni correction after one-way ANOVA) to pinpoint exactly which group is different (Bland & Altman, 1995).

For post-hoc multiple comparisons after a chi-squared test, the Marascuilo procedure was used. The procedure involves three steps. Assuming sample sizes of n_i (i=1, 2, ..., k) from k populations, the first step is to compute the differences ($p_i - p_j$) (where i is not equal to j) among all $\frac{k(k-1)}{2}$ pairs of proportions. The absolute values of these differences are the test statistics. The second step is to pick a significance level (95% or α of 5%) and compute the corresponding critical values for the Marascuilo procedure from the equation:

$$r_{ij} = \sqrt{\chi^2_{\alpha;k-1}}\sqrt{\frac{p_i(1-p_i)}{n_i} + \frac{p_j(1-p_j)}{n_j}}$$

The third step is to compare each of the $\frac{k(k-1)}{2}$ test statistics against its corresponding critical r_{ij} value. Those pairs that have a test statistic that exceeds the critical value are significant at the α level (Marascuilo, 1966).

Because most of the continuous variables in the data collected were not normally distributed even after a range of possible transformations, medians (and interquartile ranges) were used to describe them and hence the Kruskal-Wallis test was used to examine differences. StatsDirect, Version 2.3.8, (StatsDirect, Cheshire, UK) was used to compute post-hoc multiple comparisons for Kruskal-Wallis and the Dwass-Steel-Crichlow-Fligner method, which is used in most situations, is reported here. In subsequent chapters, this same analytical approach is used.

4.3 Results

4.3.1 Description of population covered

Coverage of the community survey was high with more than 97% of all homesteads agreeing to be enumerated in all districts. In all districts save Makueni, the target

population of 25,000 people was attained. Overall, the survey covered about 103,270 persons in the four districts and the first round of survey work was completed in the field within six weeks. There were between two to three households per homestead. The average homestead had approximately six sleeping rooms and an equivalent number of beds or sleeping mats. 9,272 homesteads with 18,983 resident children under five years of age were visited. Forty-six children were erroneously recruited for the childhood fever module as their dates of birth indicated they were older than five years; these were excluded from subsequent analysis (Table 4.4).

Table 4.4: Basic characteristics of the study populations in four districts of Kenya.

	Greater Kisii	Kwale	Bondo	Makueni	Total
Number of homesteads that Refused Absent/deserted Data missing	 2 1 0	 8 38 9	 3 32 6	 12 50 3	 25 121 18
Total number of homesteads sampled (coverage)	1,840 (99.8%)	2,262 (97.6%)	2,753 (98.5%)	2,417 (97.4%)	9,272 (98.3%)
Total population sampled	25,242	27,446	27,272	23,310	103,270
Total number of resident children aged < 5 years	4,949	5,412	4,756	3,866	18,983
Average number of homes per homestead	3.0	2.4	2.6	1.7	2.4
Average number of sleeping rooms per homestead	8.2	5.2	5.3	4.6	5.7
Average number of beds/sleeping mats per homestead	7.8	6.1	6.0	5.3	6.2
Number of children aged < 5 years sampled for detailed fever survey	1,425	1,627	1,644	1,591	6,287
Number of children erroneously recruited and subsequently found to be >= 5 years	5	16	16	9	46

4.3.2 Children with fever

6,287 mothers or guardians were interviewed about fever among their children in the preceding 14 days. Mothers or guardians reported a recent fever among 2,655 children (42.4%). The male-to-female ratio of children with reported fevers was 1.12:1. Overall, the median age of febrile patients was 26 months (Inter quartile range (IQR): 16, 40). Of the

children who had reported a fever in the 14-day recall period, 1,090 (17.3%) still had a fever on the day of the interview. The median duration of resolved fevers in last two weeks was four days (IQR: 3, 7). There were significant differences between districts both in fever prevalence in the recall period (χ^2=513.6, df=3, p<0.001, no two districts were alike using the Marascuilo procedure at p=0.05) and reported fevers on the day of interview (χ^2=241.4, df=3, p<0.001, no two districts were alike using the Marascuilo procedure at p=0.05). These differences seemed to mirror the district malaria ecologies with Makueni, an area of semi-arid, acute seasonal malaria reporting the lowest period prevalence of fevers (20.8%); Bondo, an area of intense perennial transmission reporting the highest (59.3%) and the other districts in-between (Table 4.5).

Table 4.5: Basic indicators describing 6,287 children under five years of age interviewed about fever in the previous 14 days in four districts of Kenya.

	Greater Kisii	Kwale	Bondo	Makueni	Total
Number interviewed about fever	1,425	1,627	1,644	1,591	6,287
Number with fever over last 14 days (%)	581 (40.8%)	768 (47.2%)	975 (59.3%)	331 (20.8%)	2,655 (42.2%)
Number with fever on day of survey (%)	291 (20.4%)	252 (15.5%)	441 (26.8%)	106 (6.7%)	1,090 (17.3%)
Urban interviews	99	304	103	86	592
Rural interviews	1,326	1,323	1,541	1,505	5,695
Fever prevalence among urban children (%)	36 (36.4%)	134 (44.1%)	58 (56.3%)	36 (41.9%)	264 (44.6%)
Fever prevalence among rural children (%)	545 (41.1%)	634 (47.9%)	917 (59.5%)	295 (19.6%)	2,391 (42.0%)
Male: Female ratio of fevers	1.25:1	1.21:1	0.98:1	1.14:1	1.12:1
Median age of children with fever [IQR: 25%, 75%]	27 [16, 40]	24 [16, 37]	27 [17, 42]	27 [15, 40]	26 [16, 40]
Median duration of resolved fevers in days [IQR: 25%, 75%]	5 [3, 7]	4 [3, 7]	4 [3, 7]	3 [2, 7]	4 [3, 7]
Percent of all febrile children who accessed any source of intervention	448 (77.1%)	529 (68.9%)	682 (69.9%)	249 (75.2%)	1,908 (71.9%)

4.3.3 Treatment actions

In this and subsequent sections, the term *public formal sector* implies GoK health facilities, Mission and NGO facilities and Community Health Workers (CHWs) which are essentially not-for-profit. Mission and NGO facilities have been classified as "public" formal providers because in Kenya these are largely run as *not-for-profit* facilities and indeed *health personnel (with formal training)* in this sector are either seconded from the Ministry of Health or directly employed by Missions and NGOs using funds provided by bilateral and multilateral donors or charities (Koinange, 1996). *Private formal sector* implies for-profit private clinics and hospitals. *Retail sector* implies general retailers, pharmacies, and itinerant vendors. *"Other" actions* are those involving homemade remedies, self-medication with western drugs within the home and use of traditional healers. Table 4.6 shows a summary of the first actions taken for the 2,655 reported fevers in the four districts. Overall, 28.1% of fevers were reportedly untreated. A test of proportions showed that there was a significant difference between fever treatment rates in the districts (χ^2=14.9, df=3, p=0.002, Marascuilo procedure reveals Greater Kisii different from Kwale and from Bondo at p=0.05) and between rural and urban populations (χ^2=5.5, df=1, p=0.019). For fevers where an action was reportedly taken, the commonest actions were treatment at public formal facilities (29.9% of fevers) or treatment using the retail sector (26.0%).

The use of the retail sector was significantly higher in Makueni than in all other districts (χ^2=21.6, df=3, p<0.001, Marascuilo procedure reveals Makueni different from all other districts at p=0.05). Further, Makueni had a higher proportion of fevers treated at private formal facilities than all the other districts (χ^2=20.7, df=3, p<0.001, Marascuilo procedure reveals Makueni different from all other districts). Treatment through prayers, homemade remedies, traditional healers, or self-medication with western drugs available in the home was 7.0 %. There were no significant differences in the use of public formal facilities

between rural and urban populations (30.1 versus 26.5%, χ^2=1.5, df=1, p=0.225) or in the use of the retail sector between rural and urban communities (25.8 versus 27.7%, χ^2=0.4, df=1, p=0.516). However, urban populations were more likely to use private formal facilities than were rural populations (χ^2=44.1, df=1, p<0.001) and rural populations more likely to resort to actions within the home than were urban populations (χ^2=5.8, df=1, p=0.016).

Table 4.6: First action taken for 2,655 fevers reported over the last 14 days in children less than 5 years of age in four districts in Kenya.

Action taken	Greater Kisii Number of fevers (%)	Kwale Number of fevers (%)	Bondo Number of fevers (%)	Makueni Number of fevers (%)	Rural Number of fevers (%)	Urban Number of fevers (%)	Total Number of fevers (%)
No action reported	133 (22.9%)	239 (31.1%)	293 (30.1%)	82 (24.8%)	689 (28.8%)	58 (22.0%)	747 (28.1%)
Public formal*	218 (37.5%)	219 (28.5%)	286 (29.3%)	66 (19.9%)	719 (30.1%)	70 (26.5%)	789 (29.9%)
Retail sector†	142 (24.4%)	206 (26.8%)	224 (23.0%)	118 (35.7%)	617 (25.8%)	73 (27.7%)	690 (26.0%)
Private formal‡	42 (7.2%)	62 (8.1%)	88 (9.0%)	52 (15.7%)	190 (8.0%)	54 (20.5%)	244 (9.2%)
Other actions§	46 (7.9%)	42 (5.5%)	84 (8.6%)	13 (3.9%)	176 (7.4%)	9 (3.4%)	185 (7.0%)
Total	581	768	975	331	2391	264	2,655

* GoK clinics and hospitals, not-for-profit clinics and hospitals, and Community Health Workers (CHW)
† General retail shops, drug vendors and pharmacies
‡ Private for-profit clinics and hospitals
§ Homemade remedies, prayers, self-medication with western pharmaceuticals in the home, and traditional healers

4.3.4 Treatment costs

1,712 fevers were analysed for drug and transport costs of first actions. Over 85% of children paid for drugs in all facility types and among urban and rural populations. Approximately 20% of those who used GoK clinics paid for transport to these facilities and twice as many paid for transport to GoK hospitals, consistent with the fact that the latter are more distant from most households. Urban populations were twice as likely to pay for transport to GoK clinics than were rural populations (χ^2=13.6, df=1, p<0.001), but less

likely to pay for transport to GoK hospitals than were rural populations (χ^2=3.9, df=1, p=0.048), consistent with the fact that GoK clinics are mostly located in rural areas and GoK hospitals in urban areas. The same pattern was evident for Mission and NGO facilities and private facilities as well: Mission and NGO clinics were more accessible than Mission and NGO hospitals (17 versus 30%) and private clinics more accessible than private hospitals (16% versus 75%). The retail sector, Bamako Initiatives (BI) and Community Health Workers (CHWs) remained the most accessible in terms of distance; less than 10% of those who used these facilities paid for transport (Table 4.7).

Table 4.8 shows the median costs associated with drugs and transport for fevers where a cost was incurred. Overall, the pattern in costs of drugs was that private clinics charged the highest amount (median KES 150, inter-quartile range (IQR) 50, 250), whereas cost of drugs at retail outlets was the lowest (median KES 17, IQR 7, 50). GoK hospitals, Mission and NGO clinics, and hospitals charged 100 KES for drugs. In contrast, GoK clinics charged almost half what the GoK hospitals charged (60 versus 100 KES).

There were significant differences in costs of drugs between the districts. Private hospitals were reportedly used in only one district, Kwale, while Mission and NGO hospitals were used in Greater Kisii and Bondo only. For the remaining facility types where it was possible to make a head-to-head comparison across the districts, costs of drugs were significantly higher in GoK clinics in Greater Kisii and Kwale than in Bondo (Kruskal Wallis=12.7, df=3, p=0.005). There were no significant differences between the costs of drugs obtained from Mission and NGO clinics in the districts (Kruskal Wallis=4.8, df=3, p=0.188). BI sites and CHWs in Kwale and Bondo charged the least for drugs (12 and 40 KES, respectively), compared to Greater Kisii and Makueni (110 and 120 KES, respectively, Kruskal Wallis=15.3, df=3, p=0.016). Drugs obtained from GoK hospitals in Greater Kisii were significantly costlier than those obtained from the same facilities in

Kwale or Bondo (Kruskal Wallis=9.9, df=3, p=0.019). Drugs obtained from retailers in Greater Kisii were almost twice the price of those obtained from Kwale and Makueni (25 KES versus 14 and 11, respectively) and those from Kwale almost half of Bondo (Kruskal Wallis=16.3, df=3, p=0.001). Private sector clinics in Bondo charged the lowest for drugs (80 KES) while other districts charged at least twice as much from these providers (Kruskal Wallis=22.2, df=3, p<0.001).

Rural populations paid significantly less for drugs obtained from GoK clinics and private clinics than did their urban counterparts (Kruskal Wallis=5.2, df=1, p=0.023 and Kruskal Wallis=13.6, df=1, p<0.001, respectively). There were no differences in cost of drugs between rural and urban populations in Mission and NGO clinics ((Kruskal Wallis=1.9, df=1, p=0.163), GoK hospitals (Kruskal Wallis=0.2, df=1, p=0.657), in the retail sector (Kruskal Wallis=2.0, df=1, p=0.153), and in private hospitals (Kruskal Wallis <0.1, df=1, p>0.999) (Table 4.8).

Table 4.7: Proportion of children under five years who paid for treatment and transport in the various sectors for first action taken for 1,712* fevers treated at different sources in four districts in Kenya.

	Greater Kisii		Kwale		Bondo		Makueni		Rural		Urban		Total	
Facility	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**
GoK clinics	92.7% (140/151)	19.2% (29/151)	96.0% (145/151)	26.5% (40/151)	90.3% (177/196)	17.3% (34/196)	96.1% (49/51)	5.9% (3/51)	92.8% (474/511)	17.6% (90/511)	97.4% (37/38)	42.1% (16/38)	93.1% (511/549)	19.3% (106/549)
Mission & NGO clinics	91.7% (11/12)	0 (0/12)	100.0% (6/6)	33.3% (2/6)	100.0% (10/10)	20.0% (2/10)	100.0% (8/8)	25.0% (2/8)	96.8% (30/31)	16.1% (5/31)	100.0% (5/5)	20.0% (1/5)	97.2% (35/36)	16.7% (6/36)
BI & CHWs	100.0% (7/7)	14.3% (1/7)	100.0% (11/11)	0 (0/11)	97.4% (37/38)	10.5% (4/38)	100.0% (3/3)	0 (0/3)	98.3% (57/58)	8.6% (5/58)	100.0% (1/1)	0 (0/1)	98.3% (58/59)	8.5% (5/59)
GoK hospitals	97.6% (40/41)	53.7% (22/41)	100.0% (47/47)	29.8% (14/47)	91.3% (21/23)	60.9% (14/23)	100.0% (3/3)	0 (0/3)	86.9% (86/99)	44.4% (44/99)	96.2% (25/26)	23.1% (6/26)	97.4% (111/114)	43.9% (50/114)
Mission & NGO hospitals	66.7% (2/3)	66.7% (2/3)	na	na	100.0% (17/17)	23.5% (4/17)	na	na	95.0% (19/20)	30.0% (6/20)	na	na	95.0% (19/20)	30.0% (6/20)
Retail sector	97.2% (138/142)	11.3% (16/142)	99.5% (205/206)	8.3% (17/206)	99.6% (223/224)	11.2% (25/224)	99.2% (117/118)	4.2% (5/118)	98.9% (610/617)	9.7% (60/617)	100.0% (73/73)	4.1% (3/73)	99.0% (683/690)	9.1% (63/690)
Private clinics	95.2% (40/42)	16.7% (7/42)	100.0% (58/58)	27.6% (16/58)	98.9% (87/88)	14.8% (13/88)	100.0% (52/52)	5.8% (3/52)	98.4% (185/188)	18.1% (34/188)	100.0% (52/52)	9.6% (5/52)	98.8% (237/240)	16.3% (39/240)
Private Hospitals	na	na	100% (4/4)	75.0% 3/4	na	na	na	na	100.0% (2/2)	100.0% (2/2)	100.0% (2/2)	50.0% (1/2)	100.0% (4/4)	75.0% (3/4)

* 11 children who presented with fever, but were subsequently admitted to hospital as inpatients excluded (4 Kisii, 4 Kwale, 2 Bondo and 1 Makueni)

† na: facility not used

Table 4.8: Median treatment and transport costs (Inter-quartile range) in Kenya Shillings (KES*) of treated fevers where a cost was incurred (n=1658 for drugs and 278 for transport).

	Greater Kisii		Kwale		Bondo		Makueni		Rural		Urban		Total	
Facility	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**	**Drugs**	**Transport**
GoK clinics	70 [40, 150]	30 [20, 60]	70 [40, 110]	35 [20, 65]	50 [30, 100]	40 [30, 60]	55 [30, 100]	60 [50, 60]	60 [30, 110]	40 [20, 60]	90 [55, 150]	35 [20, 40]	60 [30, 110]	40 [20, 60]
Mission & NGO clinics	90 [20, 150]	0	175 [100, 200]	40 [40, 40]	58.5 [35, 150]	95 [50, 140]	160 [94, 200]	50 [40, 60]	100 [35, 180]	50 [40, 60]	200 [135, 200]	40 [40, 40]	100 [40, 200]	45 [40, 60]
BI & CHWs	110 [55, 380]	120 [120, 120]	12 [8, 22]	0	40 [25, 120]	45 [40, 60]	120 [40, 240]	0	40 [20, 120]	50 [40, 70]	40 [40, 40]	0	40 [20, 120]	50 [40, 70]
GoK hospitals	135 [60, 270]	30 [20, 70]	80 [30, 180]	40 [30, 60]	50 [30, 120]	45 [20, 100]	250 [20, 295]	0	80 [40, 200]	40 [20, 80]	100 [40, 250]	20 [20, 30]	100 [40, 200]	40 [20, 80]
Mission & NGO hospitals	350 [250, 450]	110 [20, 200]	na	na	100 [30, 150]	40 [35, 100]	na	na	100 [30, 250]	40 [30, 160]	na	na	100 [30, 250]	40 [30, 160]
Retail sector	24.5 [8, 70]	20 [20, 50]	14 [6, 35]	40 [20, 80]	20 [10, 55]	60 [40, 100]	11 [7, 36]	150 [100, 240]	16 [7, 50]	50 [20, 100]	20 [8, 67]	20 [20, 60]	17 [7, 50]	50 [20, 100]
Private clinics	180 [55, 250]	40 [20, 100]	200 [130, 270]	55 [35, 80]	80 [30, 150]	40 [20, 100]	170 [70, 200]	20 [20, 40]	120 [50, 200]	40 [20, 80]	200 [135, 280]	60 [20, 70]	150 [50, 250]	40 [20, 80]
Private Hospitals	na	na	70 [35, 145]	50 [30, 80]	na	na	na	na	70 [50, 90]	40 [30, 50]	110 [20, 200]	80 [80, 80]	70 [35, 145]	40 [20, 80]

* 78.6 KES equivalent to 1 US$ on December 31, 2001 (last working day)

† 11 children who presented with fever, but were subsequently admitted to hospital as inpatients excluded (4 Kisii, 4 Kwale, 2 Bondo and 1 Makueni)

‡ na: facility not used

4.3.5 Drugs used to manage fever and their sources

Of the 1,908 fevers where any intervention was sought, 1,805 (94.6%) involved the use of western-style medications. 2,888 western-style medications were dispensed or administered for reported first actions (Table 4.9). The most widely dispensed classes of medications were the AP (52.1%) and the AM drugs (30.5%). Across all types of treatment facilities, the most widely accessed AM drugs were SP combinations (37.7% of AM drugs) and amodiaquine (AQ, 31.3%). Two hundred and forty (8.3%) medications could not be identified from drug charts or recalled by the respondents and at least 60% of these were obtained from the GoK facilities. There were no significant differences between rural and urban populations in encounters with AP (χ^2=0.6, df=1, p=0.438), AQ (χ^2=0.1, df=1, p=0.750), CQ (χ^2<0.1, df=1, p=0.906), QN (χ^2=2.0, df=1, p=0.154), SP (χ^2=0.9, df=1, 0.337), or with unknown drugs (χ^2=2.7, df=1, p=0.103). However, urban populations were more likely to encounter a non-AM or AP drug than were their rural counterparts (χ^2=12.3, df=1, p<0.001).

Table 4.10 shows drug use from an illness perspective (as opposed to product perspective in 4.9). Again, there were no significant differences in the patterns of drug use between rural and urban populations except in the use of non-AM or AP drugs as in Table 4.9 (χ^2=10.7, df=1, p=0.001). With regard to use of AM drugs, overall, 804 fevers (30.3%) were treated with at least one AM drug, and 72 fevers (2.7%) were treated with more than one AM. The most commonly used AM drug classes were from the SP group (12.1% of fevers) and AQ (9.7% of fevers). Most of the AM treated fevers occurred in the GoK facilities (46.9% of AM treated fevers). The highest AM treatment rates were found among fevers treated through the GoK facilities and Mission and NGO facilities (56.3% and 51.8% , respectively). Of fevers treated through private clinics, retail outlets or with home remedies, 49.2%, 32.9%, and 33.7% , respectively received an AM drug. Use of SP drugs rather than other AM drugs was also more common in the GoK and Mission sectors. Of

377 fevers given an AM drug in the GoK sector, 45.6% received an SP drug; 41.4% of AM treated fevers in the Mission and NGO sector received SP in contrast to 40.0%, 30.8%, and 13.8%, respectively, for those treated first through private clinics, retail outlets, or with home-based treatments. The commonest AM drug class used in the retail sector was AQ (40.5% of AM treated fevers in the retail sector).

Tables 4.11 and 4.12 show the types of AM and AP drugs used at home or purchased from the retail sector to manage fever. These were considered because drugs accessed from other sectors (e.g. the public formal sector) remain largely unknown to patients, but those purchased by patients are more likely to be identified by them. Overall, 12 brands of SP, 8 of AQ and 6 of CQ, were reportedly used within the home or purchased from the retail sector. Although there were many brands reportedly used, in most cases some brands seemed to predominate: over 60% of encounters with SP were with Fansidar® (Hoffmann La Roche. Switzerland) and Falcidin® (Cosmos Limited, Kenya); over 60% of encounters with AQ were with Malaratab® (Cosmos Limited, Kenya) and Amobin® (Regal Pharmaceuticals, Kenya), and over 80% of encounters with CQ were with unbranded CQ and with Malaraquin® (GlaxoSmithKline, UK). All encounters with QN were with unbranded generic QN (Table 4.11). The data on AM brand used are used more elaborately in Section 7.3 to see how differential brand use, combined with drug quality, and adherence to dosage regimen affect effectiveness. For AP drugs, overall, over 60% of encounters were with paracetamol: Panadol ya Watoto® (GlaxoSmithKline, UK), Panadol Extra® (GlaxoSmithKline, UK) and generic unbranded paracetamol. Of particular concern is the fact that aspirin and other nonsteroidal anti-inflammatory drugs (ibuprofen) were reportedly used in approximately 25% of the fevers treated at home or through shop-bought drugs, although these are contra-indicated in children below 12 years of age.

Table 4.9: Sources of 2,888 western pharmaceuticals dispensed or administered to 1,805* febrile children under five in four districts in Kenya.

Drug Class	Bamako Initiatives	Drugs at home	GoK health Facilities	Mission & NGO health facilities	Private clinics and hospitals	Retail sector	Rural	Urban	Total
Antipyretics	53 (61.6%)	68 (61.8%)	503 (42.5%)	52 (54.2%)	197 (45.6%)	631 (64.4%)	1,344 (52.3%)	160 (50.0%)	1,504 (52.1%)
Amodiaquine	3 (3.5%)	15 (13.6%)	120 (10.1%)	9 (9.4%)	34 (7.9%)	95 (9.7%)	247 (9.6%)	29 (9.1%)	276 (9.6%)
Chloroquine	4 (4.7%)	8 (7.3%)	88 (7.4%)	7 (7.3%)	32 (7.4%)	64 (6.5%)	180 (7.0%)	23 (7.2%)	203 (7.0%)
Other AM‡	1 (1.2%)	0	1 (0.1%)	0	0	0	2 (0.1%)	0	2 (0.1%)
Quinine	1 (1.2%)	2 (1.8%)	39 (3.3%)	4 (4.2%)	17 (3.9%)	11 (1.1%)	62 (2.4%)	12 (3.8%)	74 (2.6%)
Sulfur-pyrimethamine	14 (16.3%)	4 (3.6%)	176 (14.9%)	12 (12.5%)	49 (11.3%)	72 (7.4%)	296 (11.5%)	31 (9.7%)	327 (11.3%)
Non AM/AP†	3 (3.5%)	9 (8.2%)	112 (9.5%)	8 (8.3%)	58 (13.4%)	72 (7.4%)	216 (8.4%)	46 (14.4%)	262 (9.1%)
Unknown	7 (8.1%)	4 (3.6%)	145 (12.3%)	4 (4.2%)	45 (10.4%)	35 (3.6)	221 (8.6%)	19 (5.9%)	240 (8.3%)
Total	86	110	1,184	96	432	980	2,568	320	2,888

*Excludes four children who went to GoK facilities but whose prescriptions were not filled.
†Non-AM/AP imply drugs such as antibiotics. These were given a single code and were not identified by name or chemical class.
‡Other AM: halofantrine suspension.

Table 4.10: Access to various drug classes among 1,805* febrile children under five in four districts in Kenya as a proportion of fevers treated from each source.

Drug Class	Bamako Initiatives	Drugs at home	GoK health Facilities	Mission & NGO health facilities	Private clinics and hospitals	Retail sector	Rural	Urban	Total
Antipyretics	41 (69.5%)	59 (68.6%)	434 (64.8%)	43 (76.8%)	167 (68.4%)	538 (78.0%)	1,159 (48.5%)	128 (48.5%)	1,287 (48.5%)
Antimalarials	22 (37.3%)	29 (33.7%)	377 (56.3%)	29 (51.8%)	120 (49.2%)	227 (32.9%)	718 (30.0%)	86 (32.6%)	804 (30.3%)
Sulfur-pyrimethamine	14 (23.7%)	4 (4.7%)	172 (25.7%)	12 (21.4%)	48 (19.7%)	70 (10.1%)	290 (12.1%)	30 (11.4%)	320 (12.1%)
Amodiaquine	3 (5.1%)	15 (17.4%)	109 (16.3%)	9 (16.1%)	30 (12.3%)	92 (13.3%)	231 (9.7%)	27 (10.2%)	258 (9.7%)
Chloroquine	4 (6.8%)	8 (9.3%)	86 (12.8%)	7 (12.5%)	31 (12.7%)	60 (8.7%)	173 (7.2%)	23 (8.7%)	196 (7.4%)
Quinine	1 (1.7%)	2 (2.3%)	39 (5.8%)	4 (7.1%)	17 (7.0%)	11 (1.6%)	62 (2.6%)	12 (4.5%)	74 (2.8%)
Other AM†	1 (1.7%)	0	1 (0.1%)	0	0	0	1 (<0.1%)	1 (0.4%)	2 (0.1%)
Non AM/AP‡	2 (3.4%)	7 (8.1%)	90 (13.4%)	7 (12.5%)	48 (19.7%)	61 (8.8%)	180 (7.5%)	35 (13.3%)	215 (8.1%)
Unknown	7 (11.9%)	3 (3.5%)	122 (18.2%)	3 (5.4%)	39 (16.0%)	27 (3.9%)	185 (7.7%)	16 (6.1%)	201 (7.6%)
Total	59	86	670	56	244	690	2,391	264	2,655

*Excludes four children who went to GoK facilities but whose prescriptions were not filled.
†Non-AM/AP imply drugs such as antibiotics. These were given a single code and were not identified by name or chemical class.
‡Other AM: halofantrine suspension.

Table 4.11: Brands of 271 antimalarial drugs used at home or purchased from the retail sector by 256 febrile children under five in four districts in Kenya expressed as the percent encounter with a brand as a function of the total in each AM class. T implies tablets and S, suspensions. Asterix on T or S indicates products not registered with the PPB up to and including May 31st 2002.

Products	Greater Kisii	Kwale	Bondo	Makueni	Total	Number of fevers
SP						
Amalar® (T)	0	0	2 (8.7%)	0	2 (2.6%)	2 (2.7%)
Falcidin® (T&S)	2 (8.0%)	2 (13.3%)	1 (4.3%)	2 (15.4%)	7 (9.2%)	7 (9.5%)
Falcigo® (S*)	0	0	0	2 (15.4%)	2 (2.6%)	2 (2.7%)
Falcistat® (T)	0	0	0	1 (7.7%)	1 (1.3%)	1 (1.4%)
Fansidar® (T)	17 (68.0%)	7 (46.7%)	14 (60.9%)	5 (38.5%)	43 (56.6%)	43 (58.1%)
Kelfalin® (S)	1 (4.0%)	0	0	0	1 (1.3%)	1 (1.4%)
Medifan® (S*)	3 (12.0%)	1 (6.7%)	1 (4.3%)	0	5 (6.6%)	5 (6.8%)
Metakelfin® (T)	2 (8.0%)	2 (13.3%)	1 (4.3%)	0	5 (6.6%)	5 (6.8%)
Nopyrin® (S*)	0	1 (6.7%)	0	0	1 (1.3%)	1 (1.4%)
Orodar® (T)	0	0	0	2 (15.4%)	2 (2.6%)	2 (2.7%)
Pyralfin® (S*)	0	0	0	1 (7.7%)	1 (1.3%)	1 (1.4%)
SP unspecified (T)	0	1 (6.7%)	3 (13.0%)	1 (7.7%)	5 (6.6%)	5 (6.8%)
Unidar® (T*)	0	1 (6.7%)	0	0	1 (1.3%)	1 (1.4%)
AQ						
Amobin® (T&S*)	12 (32.4%)	1 (4.3%)	4 (10.8%)	0	17 (15.5%)	16 (15.0%)
AQ unspecified (T)	1 (2.7%)	1 (4.3%)	6 (16.2%)	2 (15.4%)	10 (9.1%)	10 (9.3%)
Betaquine® (T*)	0	1 (4.3%)	2 (5.4%)	2 (15.4%)	5 (4.5%)	5 (4.7%)
Camoquin® (T&S*)	2 (5.4%)	2 (8.7%)	1 (2.7%)	2 (15.4%)	7 (6.4%)	7 (6.5%)
Emoquin® (S)	1 (2.7%)	1 (4.3%)	2 (5.4%)	0	4 (3.6%)	4 (3.7%)
Falciquin® (S*)	1 (2.7%)	2 (8.7%)	2 (5.4%)	0	5 (4.5%)	5 (4.7%)
Malaramed® (S*)	1 (2.7%)	0	0	0	1 (0.9%)	1 (0.9%)
Malaratab® (T&S)	18 (48.6%)	15 (65.2%)	19 (51.4%)	7 (53.8%)	59 (53.6%)	58 (54.2%)
Uniquin® (T&S)	1 (2.7%)	0	1 (2.7%)	0	2 (1.8%)	2 (1.9%)
CQ						
CQ unspecified (T)	1 (25.0%)	10 (31.3%)	19 (73.1%)	4 (40.0%)	34 (47.2%)	34 (50.0%)
Dawaquin® (T)	0	3 (9.4%)	0	6 (60.0%)	9 (12.5%)	9 (13.2%)
Dawaquin junior® (S*)	0	1 (3.1%)	0	0	1 (1.4%)	1 (1.5%)
Homaquin® (T)	0	4 (12.5%)	1 (3.8%)	0	5 (6.9%)	5 (7.4%)
Malaraquin® (T*)	2 (50.0%)	14 (43.8%)	5 (19.2%)	0	21 (29.2%)	21 (30.9%)
Oroquin® (T)	1 (25.0%)	0	0	0	1 (1.4%)	1 (1.5%)
Phinaquine® (S)	0	0	1 (3.8%)	0	1 (1.4%)	1 (1.5%)
QN						
QN unspecified (T)	0	3 (100.0%)	10 (100.0%)	0	13 (100.0%)	13 (100.0%)

Table 4.12: Brands of 699 antipyretic drugs used at home or purchased from the retail sector by 597 febrile children under five in four districts in Kenya expressed as the percent encounter with a brand as a function of the total AP in district and overall. T implies tablets and S, suspensions.

Products	Greater Kisii	Kwale	Bondo	Makueni	Total	Number of fevers
Aspirin						
Aspirin unspecified (T)	10 (7.7%)	46 (19.8%)	3 (1.3%)	10 (8.8%)	69 (9.9%)	69 (11.6%)
Dispirin® (T)	0	1 (0.4%)	0	0	1 (0.1%)	1 (0.2%)
Junior Aspirin® (T)	0	2 (0.9%)	0	2 (1.8%)	4 (0.6%)	4 (0.7%)
Totoprin® (T)	0	0	0	2 (1.8%)	2 (0.3%)	2 (0.3%)
Aspirin, Paracetamol & Caffeine						
Action® (T)	2 (1.5%)	17 (7.3%)	1 (0.4%)	3 (2.6%)	23 (3.3%)	23 (3.9%)
APC® (T)	0	1 (0.4%)	0	0	1 (0.1%)	1 (0.2%)
Hedapan® (T)	0	0	0	1 (0.9%)	1 (0.1%)	1 (0.2%)
Hedex® (T)	0	4 (1.7%)	3 (1.3%)	1 (0.9%)	8 (1.1%)	8 (1.3%)
Mara Moja® (T)	1 (0.8%)	14 (6.0%)	2 (0.9%)	0	17 (2.4%)	17 (2.8%)
Nopen® (T)	0	3 (1.3%)	0	0	3 (0.4%)	3 (0.5%)
Ibuprofen						
Brufen® (T)	3 (2.3%)	2 (0.9%)	5 (2.2%)	1 (0.9%)	11 (1.6%)	11 (1.8%)
Ibufen® (S)	0	0	1 (0.4%)	0	1 (0.1%)	1 (0.2%)
Ibumex® (S)	3 (2.3%)	2 (0.9%)	0	0	5 (0.7%)	5 (0.8%)
Mediprofen® (S)	0	1 (0.4%)	0	0	1 (0.1%)	1 (0.2%)
Ponafen® (S)	1 (0.8%)	0	3 (1.3%)	0	4 (0.6%)	4 (0.7%)
Paracetamol						
Acemol® (T)	0	1 (0.4%)	0	0	1 (0.1%)	1 (0.2%)
Cafenol® (T)	0	1 (0.4%)	1 (0.4%)	0	2 (0.3%)	2 (0.3%)
Calpol® (S)	3 (2.3%)	24 (10.3%)	9 (4.0%)	3 (2.6%)	39 (5.6%)	39 (6.5%)
Dawanol® (T)	4 (3.1%)	1 (0.4%)	2 (0.9%)	2 (1.8%)	(0.1%)	1 (0.2%)
Panadol® (T&S)	26 (20.0%)	4 (1.7%)	23 (10.3%)	1 (0.9%)	54 (7.7%)	53 (8.9%)
Panadol ya Watoto® (T)	63 (48.5%)	56 (24.1%)	95 (42.6%)	21 (18.4%)	235 (33.6%)	235 (39.4%)
Paracetamol unspecified (T)	5 (3.8%)	17 (7.3%)	16 (7.2%)	60 (52.6%)	98 (14.0%)	98 (16.4%)
Paracetmol & Caffeine						
Cold Cap® (T)	2 (1.5%)	3 (1.3%)	2 (0.9%)	1 (0.9%)	8 (1.1%)	8 (1.3%)
Panadol Extra® (T)	6 (4.6%)	32 (13.8%)	57 (25.6%)	6 (5.3%)	101 (14.4%)	101 (16.9%)

4.3.6 Timing of treatment

Table 4.13, Figure 4.8, and Figure 4.9 show the cumulative proportions of fevers treated as a function of time across the study districts. Overall, 13.6% of fevers were treated within 24 hours. Further, 5.3% of fevers were treated with an AM within 24 hours and 14.7% within 48 hours. However, very few fevers were treated with SP, the first-line drug at the time of the survey, within 24 and 48 hours (2.3 and 6.7%, respectively). There were differences between the districts in the fever treatment rates; significantly more fevers were treated in Greater Kisii (19.6%) than in Bondo or Kwale districts within 24 hours (χ^2=29.6, df=3, p<0.001, Marascuilo procedure Greater Kisii different from Bondo and Kwale at p=0.05). In addition, more fevers in Greater Kisii were treated with an AM drug (9.6%) and with SP (5.0%), within 24 hours than in Kwale and in Bondo (χ^2=30.8, df=3, p<0.001 and 28.4, df=3, p<0.001, respectively. Marascuilo procedure Kwale and Bondo different from Greater Kisii at p=0.05).

At 48 hours, Greater Kisii had the highest treatment rate compared to the other districts (χ^2=57.8, df=3, p<0.001, Greater Kisii different from all districts using Marascuilo Procedure at p=0.05 and Kwale different from Bondo) and, the highest rates of treatment with AM at 48 hours (χ^2=52.0, df=3, p<0.001, Greater Kisii different from all districts using Marascuilo Procedure at p=0.05) and the highest rates of treatment with SP at 48 hours (χ^2=53.4, df=3, p<0.001, Greater Kisii different from all districts using Marascuilo Procedure at p=0.05). Over 48 hours, significantly more fevers in Greater Kisii were treated than in Kwale or Bondo (χ^2=14.9, df=3, p=0.002) with the district being different from Kwale and Bondo using the Marascuilo Procedure at p=0.05. The same pattern was evident for treatment with an AM over 48 hours (χ^2=21.6, df=3, p<0.001) and with SP over 48 hours (χ^2=39.7, df=3, p<0.001). There were no differences between rural and urban populations in treatment rates within 24 hours (χ^2=1.3, df=1, p=0.256), but urban

populations had higher treatment rates at 48 hours (χ^2=5.9, df=1, p=0.015) and over 48 hours (χ^2=5.5, df=1, p=0.019). However, and significantly, there were no differences between rural and urban populations in access to AM drugs within 24 (χ^2=0.3, df=1, p=0.559), 48 (χ^2=1.7, df=1, p=0.198) and over 48 hours (χ^2=0.8, df=1, p=0.385) and to SP within 24 (χ^2=0.8, df=1, p=0.371), 48 (χ^2=0.2, df=1, p=0.642) and over 48 hours (χ^2=0.1, df=1, p=0.732). The overall delay in seeking ***any*** treatment was two days for Greater Kisii (IQR: 1, 3) and Kwale (IQR: 2, 4) and three days for Bondo (IQR: 2, 5) and Makueni (IQR: 2, 4).

Table 4.13: Cumulative proportion of fevers treated with an antimalarial (AM) and with sulfur-pyrimethamine (SP) in four districts of Kenya as a function of time.

Place	Treatment	Time		
		24 hours	48 hours	Over 48 hours
Greater Kisii	Any treatment	114 (19.6%)	287 (49.4%)	448 (77.1%)
	AM	56 (9.6%)	147 (25.3%)	220 (37.9%)
	SP	29 (5.0%)	76 (13.1%)	107 (18.4%)
Kwale	Any treatment	91 (11.8%)	292 (38.0%)	529 (68.9%)
	AM	27 (3.5%)	111 (14.5%)	208 (27.1%)
	SP	12 (1.6%)	48 (6.3%)	89 (11.6%)
Bondo	Any treatment	103 (10.6%)	294 (30.2%)	682 (69.9%)
	AM	38 (3.9%)	118 (12.1%)	275 (28.2%)
	SP	10 (1.0%)	34 (3.5%)	77 (7.9%)
Makueni	Any Rx	54 (16.3%)	121 (36.6%)	249 (75.2%)
	AM	20 (6.0%)	44 (13.3%)	101 (30.5%)
	SP	10 (3.0%)	21 (6.3%)	47 (14.2%)
Rural	Any treatment	320 (13.4%)	877 (36.7%)	1702 (71.2%)
	AM	129 (5.4%)	371 (15.5%)	718 (30.0%)
	SP	57 (2.4%)	163 (6.8%)	290 (12.1%)
Urban	Any treatment	42 (15.9%)	117 (44.3%)	206 (78.0%)
	AM	12 (4.5%)	49 (18.5%)	86 (32.6%)
	SP	4 (1.5%)	16 (6.1%)	30 (11.4%)
Total	Any treatment	362 (13.6%)	994 (37.4%)	1,908 (71.9%)
	AM	141 (5.3%)	390 (14.7%)	804 (30.3%)
	SP	61 (2.3%)	179 (6.7%)	320 (12.1%)

Figure 4.8: Cumulative proportion of access to different first treatment sources among 2,655 febrile children in four districts in Kenya as a function of time. Treatment sources defined as private formal (private for profit clinics and hospitals); public formal (government, mission and NGO not-for-profit dispensaries, health centres and hospitals, community health workers); retail sector (general retail shops and pharmacies); other (western pharmaceuticals administered at home, home remedies, prayers and traditional healers). (a) Greater Kisii (green, n=581 fevers), (b) Kwale (blue, n=768 fevers), (c) Bondo (yellow, n=975 fevers) and (d) Makueni (red, n=331 fevers).

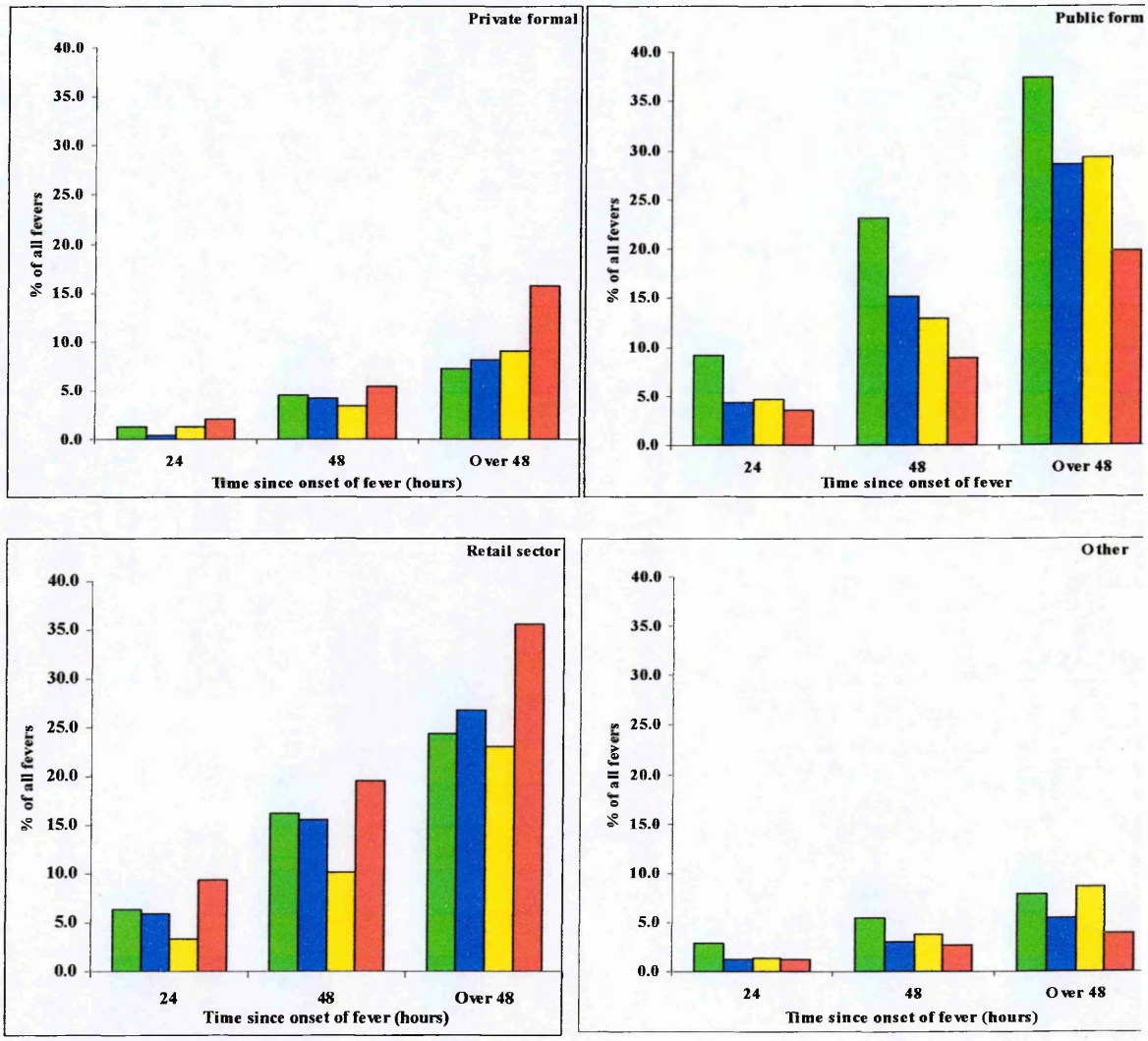
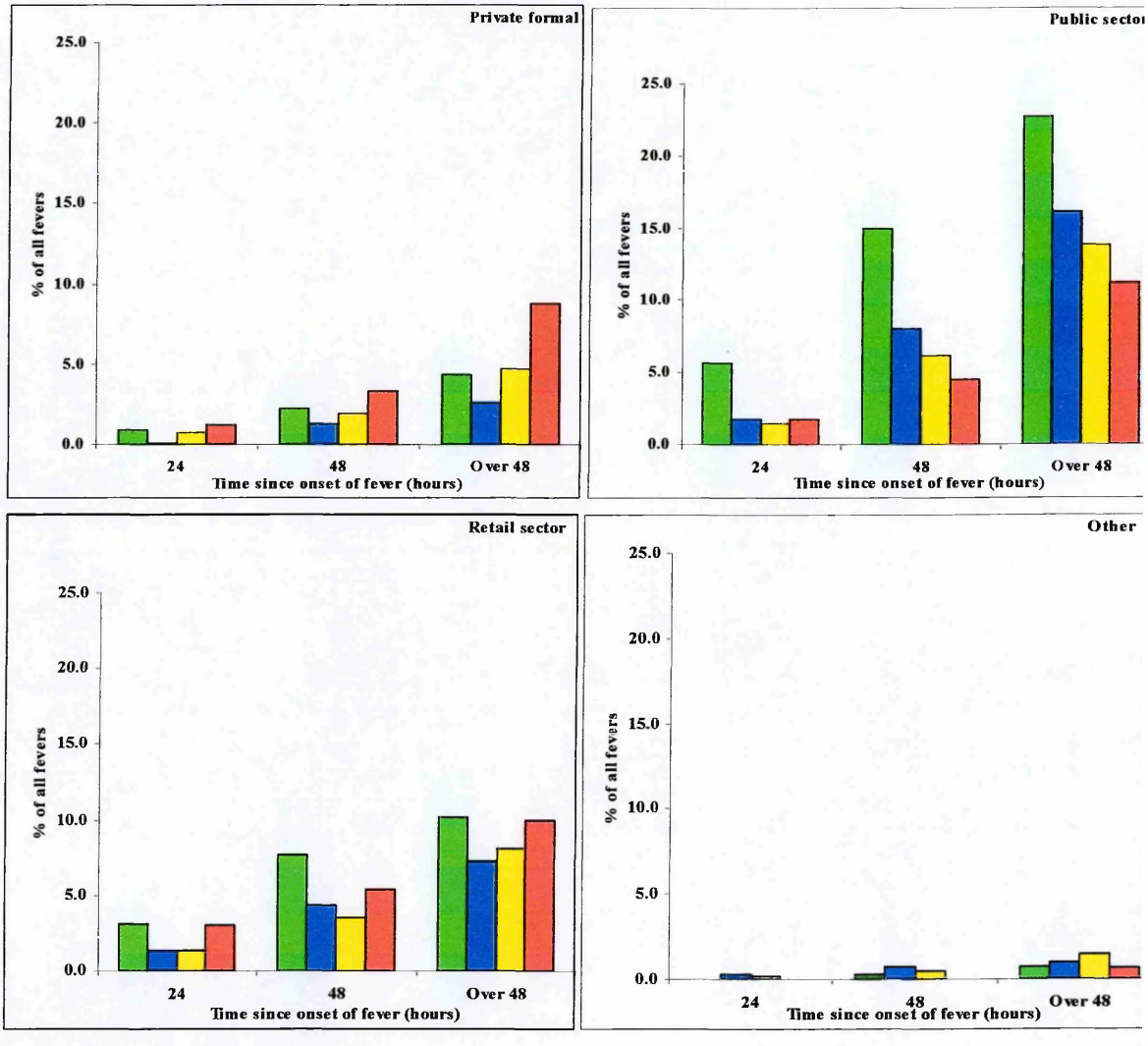


Figure 4.9: Cumulative proportion of 2,655 febrile children in four districts in Kenya who accessed at least one antimalarial drug from different sources as a function of time. Treatment sources defined as private formal (private for profit clinics and hospitals); public formal (government, mission and NGO not-for-profit dispensaries, health centres and hospitals, community health workers); retail sector (general retail shops and pharmacies); other (western pharmaceuticals administered at home, home remedies, prayers and traditional healers). (a) Greater Kisii (green, n=581 fevers), (b) Kwale (blue, n=768 fevers), (c) Bondo (yellow, n=975 fevers) and (d) Makueni (red, n=331 fevers).



4.4 Discussion

4.4.1 General observations

A number of broad observations can be made from the community survey of 6,287 children whose caretakers were interviewed about fevers in the last 14 days in the four study districts. First, reported fever was a common event among children under five. The overall period prevalence of fever among this age group was 42.2 %, which is consistent with what has been previously reported for children under five in Kenya (NCPD, 1989; 1994; 1999). Second, there were significant differences in period prevalence of fever between the four districts that seemed to mirror their distinct malaria ecologies. Third, a substantial number of fevers (42%) were treated outside the public formal sector using mostly western pharmaceuticals. Fourth, less than 3% of fevers were treated within 24 hours with the nationally recommended first-line AM drug, SP, and obtained largely from the formal public sector. Finally, access and use of AM drugs between different service providers varied between the districts sampled. These observations and their policy implications will be discussed in the following sub-sections, but first the limitations of the study are discussed.

4.4.2 Study limitations

In most studies, treatment seeking for fevers is described as a hierarchical process where caretakers or patients first seek cheaper alternatives before progressing to the formal sector in the course of the illness. Studies undertaken at formal public facilities have shown that a high proportion of fevers are first treated at home with shop-bought AM and AP drugs before presenting to the health facility (Snow *et al.*, 1992; Marsh *et al.*, 1999). It is also acknowledged that caretakers' responses to questions on health seeking are not always accurate. In a study in Malawi, Nwanyanwu *et al.* (1996) found discordance between mothers' history of use of AM drugs among their children and the results of subsequent

urine tests. A number of reasons have been postulated to try to explain these discrepancies. In some cases, the illness episode is too minor and self-limiting for the mother to recall whether or not it was treated, and when treated with what drugs (McCombie, 2002). At times, the caretakers' perception of the aims and objectives of the interview lead them to give responses that they think the interviewees want to hear (Deming *et al.*, 1989; Slutsker *et al.*, 1994; Nwanyanwu *et al.*, 1996). In this chapter, emphasis has been placed on the first actions for treatment seeking obtained through community-wide rapid household surveys, much like the demographic and health surveys. Under reporting of treatment actions might have occurred especially among the "no action" group and among fevers reportedly treated first at formal public and private facilities.

In addition, no reliable information could be obtained from the community survey on adherence to dosage regimen. This is because data collected were inadequate in the sense that only the brands used and the total amounts consumed were collected without any indication as to the period over which (and how) the products were consumed. There is therefore need for more carefully-conducted research on adherence to AM dosage regime, much like the data used for the effectiveness model in Chapter 7.

4.4.3 Sources and types of treatment

Among the study populations, only 39.1% of fevers were reported to have been treated at a formal public or private clinical facility as a first action. This suggests that most people seek treatment outside the formal health sector, which is consistent with the findings of other workers in Kenya (Section 2.5) and across Africa (Section 1.8). Although a majority of fevers were treated outside the formal public sector, the proportion treated in this way receiving any AM drug (56 versus 37%), as well as receiving the first line recommended AM drug (25 versus 13%) was higher than for those seeking treatment from any other

source. This points to the need for measures to improve prescribing practices in private sector clinics and fever management practices at home (Abuya, 2001). Further, the use of western pharmaceuticals was very high with about 95% of treated fevers being exposed to western pharmaceuticals. The most commonly used drugs were the AP and the AM drugs, an observation that has been made before in Kenya and elsewhere in Africa (Sections 2.5 and 1.8). Among the AP and AM drugs used at home or obtained from the retail sector, the most widely accessed classes were paracetamol containing products for AP, and SP and AQ products for AM. Further, among these classes, a handful of brands were mostly used. The public health implications of this finding are discussed in relation to drug quality and effectiveness in Chapter 7.

4.4.4 Timing of treatment

Results indicate that there was a median waiting period of two days (IQR: 2, 4) across the four districts to *any* form of treatment for children less than five years of age. Among children presenting to a health facility in The Gambia with malaria, Greenwood *et al.* (1987) found that the mean duration between the onset of symptoms and development of severe complications was 1.8 days, and mean duration between onset of symptoms and death was 2.8 days. Considering that roughly 40% of the paediatric fevers reported are probably malaria (Greenwood *et al.*, 1987; Brinkmann & Brinkmann, 1991), this delay in treatment seeking is of great concern. There is therefore need to encourage prompt treatment of fevers with appropriate first-line AM drugs as close to home as possible to reduce the risk of severe complications in this age group. Furthermore, more formative research is needed to understand why people delay seeking treatment to better target information, education and communication (IEC).

4.4.5 Use of antimalarial drugs and the role of the retail sector

The findings also showed that by the time of interview, only 30.8 % of reported fevers had been treated with AM drugs, 5.3% within 24 hours, and 14.7% within 48 hours. Across the districts, the public formal sector was found to be the most common source of early AM treatment with Greater Kisii having the best access to AM drugs and to SP. Better access to AM and to SP in Greater Kisii can be explained by proximity to public sector health facilities (which are best at availing these drugs, Table 4.10). Although the other districts have a more favourable health facility to population ratio (Table 4.1), over 99% of the population of Greater Kisii live within 5 km of a health facility. In contrast, 80% of the population in Bondo and only 65% of the population of Kwale and Makueni live within 5 km of a health facility (Noor *et al.*, 2003). Distance is therefore an important factor in accessing prompt, effective treatment for fever and malaria.

Outside the formal sector, the retail sector seems to have the greatest potential in improving access to AM drugs. This is because this sector is generally more accessible geographically, there are more outlets per head than the formal sector (10 retail outlets for every health facility, Table 4.1), and treatment from this source involves less time and money. However, being a requisition-based supply system rather than the government run allocation system that is amenable to restricted supply in AM drugs in line with policy (Section 3.3.1), there is a predisposition towards demand-driven choice of drugs. AQ, a second line drug is freely available and sold in shops and pharmacies in Kenya (Siringi, 2001) and the study districts are no exception (Section 5.3.4). This paradox creates a dilemma for the policy-practice interface and a better engagement of the retailers is required to restrict access to second-line treatment policy-recommended drugs (Section 5.4.1).

Approximately 33% of fevers treated at home or through the retail sector received an AM drug. This figure is comparable to a median of 38% (interquartile range (IQR) 28 to 53%) across eight districts in Kenya derived previously from a variety of studies (Section 2.5.1). Conversely, 53% of fevers treated through a formal clinic received an AM drug. This is much lower than a median of 91% (IQR 89 to 94%) previously derived for fevers treated through the formal sector in Kenya (Section 2.5.1). As explained in the study limitations, underreporting of treatment actions is not uncommon in surveys of this type and mothers are known to give incorrect answers to questions depending on the perceived purpose of the survey (Section 4.4.2).

4.4.6 Costs of drugs at government facilities

From the early independence days, through to the introduction of user charges in GoK facilities, children under five had been exempted from charges at health facilities. The fact that the majority of children under five in the community survey reportedly paid for drugs could have two, mutually reinforcing explanations. During the introduction of user charges in the 1980s and 1990s, there was a concomitant drive towards decentralisation of health services to the district level to improve efficiency and accountability at the grassroots (Owino & Munga, 1997). This policy however was marred by implementation problems (Owino, 1997; Owino & Munga, 1997; Wang'ombe, 1997) leading to confusion in the health sector as to what constitutes "official" policy and what is not. In a number of press reports, the MoH has reiterated its policy of free health-care for under fives or for specific diseases like malaria (http://www.nationmedia.com, accessed 07/12/04), but because decentralisation has entrusted the day-to-day running of facilities to DHMTs who have discretionary powers, it is possible that overlapping lines of authority sometimes result in conflicting messages, leaving each facility or district to interpret "policy" differently resulting in different waiver and exemption schemes. Another possibility is that

prescriptions made at GoK facilities are filled from the retail sector since stock-outs of essential drugs are a common occurrence in GoK facilities; therefore, guardians report having paid for drugs even when they bought them from the private sector.

4.4.7 Gap between the Abuja Target and current practice

In terms of promptness and appropriateness of AM therapy, results indicate that only 2.3% of fevers in the four communities were managed in the first 24 hours using SP, the recommended first-line therapy for uncomplicated malaria in Kenya in 2001. It is known that most treatments are incorrect or sub-optimal among populations across the continent (Section 1.8). Further, effective treatment is likely to be much lower than those who were simply treated with the correct drug (Krause & Sauerborn, 2000). In the Abuja declaration, African Heads of States committed themselves and their countries to ensuring that 60% of fevers in the continent are treated promptly within the first 24 hours with safe, effective, quality AM drugs (WHO, 2000c). If all drugs were effective for the 5.3% fevers where AM drugs were accessed in the four districts within 24 hours, there still remains a huge gap between policy and practice. To bridge this gap a major investment in improving prompt access to AM drugs through improved behaviour change initiatives and improved physical access is required if morbidity and mortality due to malaria is to be halved by the year 2010. And this is true of formal health sector as well as the retail sector.

4.4.8 Implications for ART-LUM, the new first-line policy

Although most fevers are treated outside the formal public sector, fevers treated within the public sector are more likely to receive the first-line AM drug than those treated outside this sector. The findings show that 25.7% of fevers treated through the GoK facilities and 21.4% of those treated through the Mission and NGO sectors received SP, the first-line drug in 2001. Although this figure is low compared to previous studies in Kenya (Section

2.5), the finding nonetheless has a potential for exploitation. It is proposed that the new AM policy (ART-LUM) will be introduced in a staggered manner and will be distributed within the GoK and Mission and NGO sectors within the first two years of implementation (Section 2.5.2). Barring stock-outs in these two sectors, it means that more fevers presenting to public sector facilities will have better access to ART-LUM than fevers presenting to the private-for-profit sector and the retail sector since drug use in the formal sector is driven by prescription practices and that in the retail sector by patient choice. There is therefore need to encourage guardians of children below five to seek treatment for fevers and malaria in public sector health facilities. If current treatment seeking behaviour for fevers continues, almost 90% of children treated at home or through the retail sector will not have access to ART-LUM (about 10% receive first-line AM). This figure will most likely be much higher since ART-LUM is several times the cost of SP (Section 5.3.5). There is therefore a need to 1) encourage use of first-line AM drugs in the retail sector through targeted IEC materials and more specifically to 2) explore mechanisms to reduce prices of ART-LUM in the retail sector to guarantee better access to ART-LUM in this sector. The latter has been raised in a number of meetings by the DMS (Section 2.7.3.2)

Overall 8.3% of western pharmaceuticals dispensed were unknown by the respondents, almost all of these were provided by GoK facilities. This finding is hardly surprising given that caretakers at GoK facilities are rarely told what their children are suffering from nor is enough time spent in explaining medications prescribed or dispensed to them (Zurovac *et al.*, 2005). There is need to improve patient prescribing and dispensing practices in public sector health facilities to improve patient adherence to ART-LUM. This is important because ART-LUM is taken over three days and has a complex dosing interval. In

addition, ART-LUM requires fatty meals for adequate absorption to take place. Poor adherence to ART-LUM will therefore result in lower drug effectiveness (see Chapter 7).

4.5 Summary

In this chapter, data were presented on the four study districts, the characteristics of the study populations, fever management practices, and drug use patterns. The districts were found to be diverse in their literacy, poverty, and malariometric indices and in their fever management and drug use patterns. Fever was found to be a common occurrence among children under five in Kenya with significant differences between the study districts, reflecting their respective malaria transmission characteristics. There were also differences between the districts in treatment rates, access to AM drugs and to SP, the first-line drug in 2001.

Although most fevers either remained untreated or were treated outside the formal public sector, fevers treated through this sector had the highest chance of receiving an AM drug or SP. There is therefore a need to improve access to formal sector providers during the early phases of implementation of the new AM policy, ART-LUM. The retail sector was also found to be an important source of treatment for fevers close to home and efforts must be made to improve drug supply, costs and delivery in this sector so that a more uniform and equitable access to AM drugs is maintained.

Finally, a policy-practice gap was found to exist between the Abuja target and current fever management practices. This gap needs to be bridged if mortality and morbidity due to malaria is to be halved by 2010. A substantial investment in behaviour change initiatives in both the public and private sector is required. In the next chapter, the role of the retail

sector in AM service delivery and its potential for rolling back malaria will be explored in further detail.

CHAPTER 5:

Availability, range, and costs of anti-malarial drugs and other commodities in the Kenyan retail sector

5.1 Introduction

During the 2001 community survey, it was clear that the use of antimalarial (AM) and antipyretic (AP) drugs from the retail sector was common across all four study districts (Section 4.3.5) and that these findings were consistent with other studies in Kenya (Sections 2.5). Furthermore, the Division of Malaria Control (DOMC) has acknowledged that the retail sector is an important service provider for the home management of fevers (including malaria), as articulated in the Kenya National Malaria Strategy (KNMS), and is working in collaboration with partners in the health sector to explore ways to encourage appropriate drug use and provide relevant information for fever management through this sector (DOMC, 2001f). This is in line with a WHO effort to improve access to AM drugs at household levels (WHO, 2003b). Such approaches to strengthen the retail sector require careful definition of the problems of AM service delivery by this sector. This chapter describes some of the features of the retail sector in the four sentinel districts. Data are presented on: the range and prices of AM drugs in the retail sector; knowledge of retailers regarding the use of AM drugs; and availability of non-drug commodities used in the fight against malaria. The variation in accessibility to a range of AM products, prices and retailer knowledge is used to describe the potential weaknesses of this sector for fever management and ways in which these might be redressed.

5.2 Study location, design, and methods

The studies were conducted in the four districts described in Section 4.2.1.

5.2.1 Developing a national AM database

A national list of all AM drugs in the Kenyan market was developed starting August 2001 from three principal sources: two commercially available drug and medical devices price

lists (SMS, 2001; Kimotho *et al.*, 2002) and lists of registered AM drugs available at the Pharmacy and Poisons Board (PPB) of the Ministry of Health (PPB, 1996; 2001). The derived list included details of products such as brand names, dosage forms, strengths, manufacturers, trade packs, trade prices, and registration status.

For sulfur-pyrimethamine (SP) and amodiaquine (AQ) products, an attempt was made to triangulate the details of each product in the list with the manufacturers or dealers by regular correspondence via telephone, e-mail or fax. A further attempt was made to obtain samples of such products (by direct purchase) since official lists would not contain drugs that were considered to be in the country illegally. Digital photographs of oral preparations of AQ and SP were taken using a Nikon Coolpix 990 and photographs stored as JPEG files and exported into Word for Windows. This additional database was used as a visual aid for the community survey discussed earlier in Section 4.2.4.

Regular updates of AM drug ranges and prices were obtained from the two product lists and registration updates from the PPB list via regular visits to the PPB or via Kenya Gazette notices obtained from the Government Printers. This national AM database was used as a comparator for the range and prices of over-the-counter (OTC) AM products in the periphery (districts). Injections and suppositories, which would not ordinarily be available OTC, were excluded from analysis. To make the AM database temporally comparable to subsequent surveys in the districts, a period up to and including May 31 2002 was selected as the cut-off point.

5.2.2 Retail audit sample

A retail audit was carried out between May and June 2002 where the unit of study was the retail outlet. Outlets were first identified from a commercial database subsequently visited

to verify if a) they still existed; b) they still sold AM drugs or not; and c) to secure consent for a more detailed study at a later date. This exercise was followed by a more in-depth audit using a structured questionnaire (see Appendix III). Detailed steps of how the audit was carried out are given in the following sub-sections.

5.2.2.1 Retail outlet census

5.2.2.1.1 The primary database

Data on retail outlets was purchased from Research International East Africa Limited, a commercial market research organisation that carried out a retail outlet census in Kenya between 1999-2000. In this survey, outlets were positioned using hand-held Global Positioning Systems (GPS). Information was collected on a number of parameters summarised broadly thus:

Outlet Location: Location was defined in terms of administrative boundaries, longitude/latitude, and street address (where relevant). Under the first, outlets were mapped to the sub-location level. The longitude, latitude and physical or street addresses of the outlets were also recorded. A final category was that of the site profile; whether or not the outlet was in a city centre, town centre, shopping centre, next to infrastructure like main roads, railways, airports and so on.

Type of outlets: Outlets were divided into 44 types. Examples were wholesale, wholesale and retail, hypermarket, mega market, food kiosk, wines and spirits shops, open market stalls, duty free shop, chain store, self-service store, and other.

Stock details: Under this, stock type was divided into 22 categories ranging from non-alcoholic beverages (sodas, coffee, etc) to miscellaneous items like batteries and shoe polish. Each category was subdivided and coded. For instance, antimalarial drugs (stock type M) were sub-divided into tablets (1), syrups (2), and "other" (3). Stock sources were categorised into manufacturer, distributor, wholesaler, salesmen, retailers, imports, other, and each given a code.

Personnel: Details of the respondent were taken down; so were the number of employees (both full-time and part-time) and their weekly working hours.

5.2.2.1.2 Data management for sampling

Descriptive data on each outlet were used to identify outlets that stocked and sold AM or AP products at the time of the retail census (1999-2000). Data were then displayed in MapInfo (Version 6.0, 1985-2000) and physical addresses compared against correct coordinates of market centres obtained from topographic maps and GPS data from various sources (CBS, 2001a; Noor *et al.*, 2003). Any errors in positioning in 1999-2000 data were then corrected and positions of outlets redefined to the market centre. Except for pharmacies, (Category 1 outlets), all other outlets reported to be selling over-the-counter (OTC) AM and AP drugs during the census, were grouped into two categories defined by the number of fulltime sellers. A Large *duka*/shop (Category 2) was defined as a store that sold its products over the counter with more than one person serving customers during normal working hours, while a Small *duka*/shop (Category 3) was defined as any outlet having only one person serving customers during normal working hours. This categorisation was based on the fact that the busier the shop (which is an indicator of stock and its turnover) the more staff are required to serve customers. Where there was an obvious discrepancy between this criteria and the situation on the ground, a combination of this and the stock was used to reclassify category 2 and 3 outlets.

The CBS classification of urban and rural areas was used to define "urban" or "rural" outlets (Section 4.2.3). In subsequent sections therefore, the terms "rural" or "urban" outlets imply outlets found in enumeration areas (EA) considered rural or urban according to the CBS definition. Shops were assigned to their relevant EAs after the retail audit.

5.2.2.1.3 Sampling

Outlets thus identified and defined were sampled based upon the estimates of the numbers of retail outlets in each district and the expected prevalence of key parameters of interest. Calculations were done using Epi-Info, version 6.04d (Centers for Disease Control, USA). Table 5.1 shows a sample district (Greater Kisii) and estimated prevalence of key parameters derived from studies conducted in Kilifi district (Dr V Marsh, personal communication). Sample sizes were derived to achieve between 5-10% precision and 95% confidence in the parameters of interest. It was estimated that the ratio of pharmacies to large shops to small shops would be 1:2:8. A minimum of 20 pharmacies in each district were targeted (all were included if less than 20). Large *duka*s were randomly sampled to achieve a minimum of 40 outlets per district, randomisation taking care of the rural/urban divide. Where Large *Duka*s were less than 40, all were included. For smaller outlets, a random sample of 160 per district was selected, randomisation also taking care of the rural/urban divide. Overall, about two hundred and twenty (220) outlets were assessed in each district. Samples were randomly selected using a simple raffle where strips of papers with the codes of the outlets were written, folded, shuffled, and picked until the required number of outlets in each category was achieved.

Table 5.1: Sampling approaches for the Retail Audit Survey carried out in four districts of Kenya in 2002.

Parameter	Estimated prevalence (Kilifi)	e.g. Greater Kisii (Number of outlets=2002) *	Total *
Types of OTC drugs sold in private retail outlets (brand names and pharmacological groups)	50% sell AM	92-322	340-1028
Presence in shop of effective first line AM drugs:			
Within date	75%	70-252	262-836
Adequate quality	75%	70-252	262-836
Recommended type	10%	34-129	132-465
Adequately stored	60%	88-311	327-1000
Presence in shop of DOMC guidelines on use of OTC AM and AP drugs (leaflet, poster, other)	0%	-	-
Seller knows DOMC recommendations for AP use with AM drugs (e.g. SP plus paracetamol)	5%	70	265
Seller can use reference materials for dose and regime for AM and AP drugs according to age of user (drug charts on packages or other according with DOMC recommendations):			
For single dose AM regimes	50%	91-322	340-1028
For multi-dose AM regimes	20%	60-219	226-743
Seller is willing to provide information on use of OTC drugs to customers	50%	92-322	340-1028

* Figures in columns (x-y) represent required sample size for 5%-10% precision and 95% CI.

5.2.2.2 Locating outlets

Each district was visited between February 18th and May 30th 2002 to sensitise the local administration and the Ministry of Health (MoH) personnel to the aims and objectives of the study. Bondo district was visited between February 18th and March 2nd; Greater Kisii between March 3rd and 23rd; Makueni between April 23rd and May 7th; and Kwale between May 13th and 30th. In addition, each selected shop was visited to establish its precise geographical position using a hand-held GPS unit (Magellan GPS 315 or Garmin etrex) and confirm that the outlet was still retailing AM drugs. Shopkeepers were informed of the purposes of the study and asked for permission to be interviewed later. Replacements were made both at this stage and later for shops and pharmacies that had closed (n=99); were not identifiable at the district level owing to incorrect or insufficient details on the original

1999-2000 database (n=201); had no AM during recruitment (n=60); had no AM during the main survey (n=38) or where the shopkeepers refused to participate (n=5).

5.2.3 Retail audit fieldwork

A Retail Audit proforma (Appendix III) was designed and used to capture basic information on a number of parameters of interest. These were outlet's position, advertising for AM, AP and other malaria resource materials, characteristics of retailers and the outlets, brands of AM and AP drugs, pharmacological groups, wholesale source, retail prices and basic storage conditions. Information was also sought on the presence in the outlets of insecticide treated bed nets (ITN), insecticides for treating nets, insecticides for indoor residual house spraying, mosquito coils, aerosols, and repellents. In addition, information was collected on official information, education, and communication (IEC) materials from the DOMC (posters and leaflets), branded advertisements, and shopkeeper knowledge of AM doses for adult and paediatric clients (two-year olds). Questionnaires were piloted in Mtondia, Kilifi district between January 10th and 20th 2002 and revised according to problems identified by field staff and selected shopkeepers.

Twenty field workers (FWs) were recruited and trained in survey methodology using standard training manuals. All but two of the FWs had at least a first degree, mostly in the social sciences and their research experience ranged from six months to five years. FWs were trained in Nairobi for three days. Briefing notes on each data collection form were prepared before the audit and used to brief the interviewers on how to handle each question. Training included role-play and mock interviews to ensure standardised approaches.

FWs were provided with the randomly selected outlet list and asked to interview the *usual*

retailers and not those who occasionally stood in for them. Where there was more than one seller in the outlet, the longest serving seller was selected and interviewed. One of the FWs was selected as a team leader to co-ordinate fieldwork in each district. The team leader handled complaints, took corrective action, and evaluated interviewer performance and output.

Two techniques were used to ensure the quality of the data in the field: *accompaniment*, where FWs were accompanied by the supervisor in 10% of all interviews to gauge interviewer performance; *back-checking* where the team leader randomly sampled 10% of all shops and redid the interviews to ensure reproducibility of responses. In addition, all questionnaires were reviewed at the end of each day to ensure all questions had been answered and coded correctly. All completed questionnaires were re-reviewed within three days of receipt in Nairobi and any further queries returned to the districts for resolution. All data were entered twice using MS-Access 2000 developed data-entry screens, verified and cleaned as discussed previously in Section 4.2.5.

5.2.4 Statistical approaches

This has been covered in depth in Section 4.2.5. In addition, univariate and multivariate analysis was undertaken for questions on doses of AM drugs (Section 5.3.8).

5.3 Results

5.3.1 Characteristics of retail drug outlets and retailers

Figure 5.1 shows the geographic coverage of the 880 outlets audited in 2002, while the key characteristics of the audited retailers are shown in Table 5.2. There was a good geographic spread of the outlets, representative of all four districts. Four small shops (all in Bondo district) were excluded from subsequent analyses since they remained closed even after

three consecutive visits. The proportion of main sellers who were male ranged from 35.0% in Bondo to 70.0% in Kwale with significant differences between the districts (χ^2=59.4, df=3, p<0.001). Further multiple comparisons using the Marascuilo Procedure shows that Kwale district was different from all other district in this regard and Greater Kisii from Bondo (p=0.05).

Overall, a typical main seller was a 30 year-old male or female with 10 years of schooling, selling drugs at a 4.3 year-old outlet for a median 3.0 years. There were significant differences between the districts in the age of main seller (Kruskal-Wallis=43.7, df=3, p<0.001), years of schooling (Kruskal-Wallis=17.4, df=3, p=0.001), age of outlet (Kruskal-Wallis=17.4, df=3, p=0.001) and length of period the main seller worked in the outlet (Kruskal-Wallis=47.8 df=3, p<0.001). Further multiple comparisons after Kruskal-Wallis test show that Greater Kisii district differed from Kwale, Bondo, and Makueni in age of main seller, years of schooling and years of service in the outlet. For the length of time the outlet had been open, Greater Kisii differed only from Kwale and from Bondo. In terms of years of service at the retail outlet, main sellers tended to have worked longer at their outlets in Greater Kisii than Kwale or Bondo, and longer in Kwale than in Makueni (Table 5.2).

Figure 5.1: Geographical distribution of 880 retail outlets audited in 2002 in four districts of Kenya.

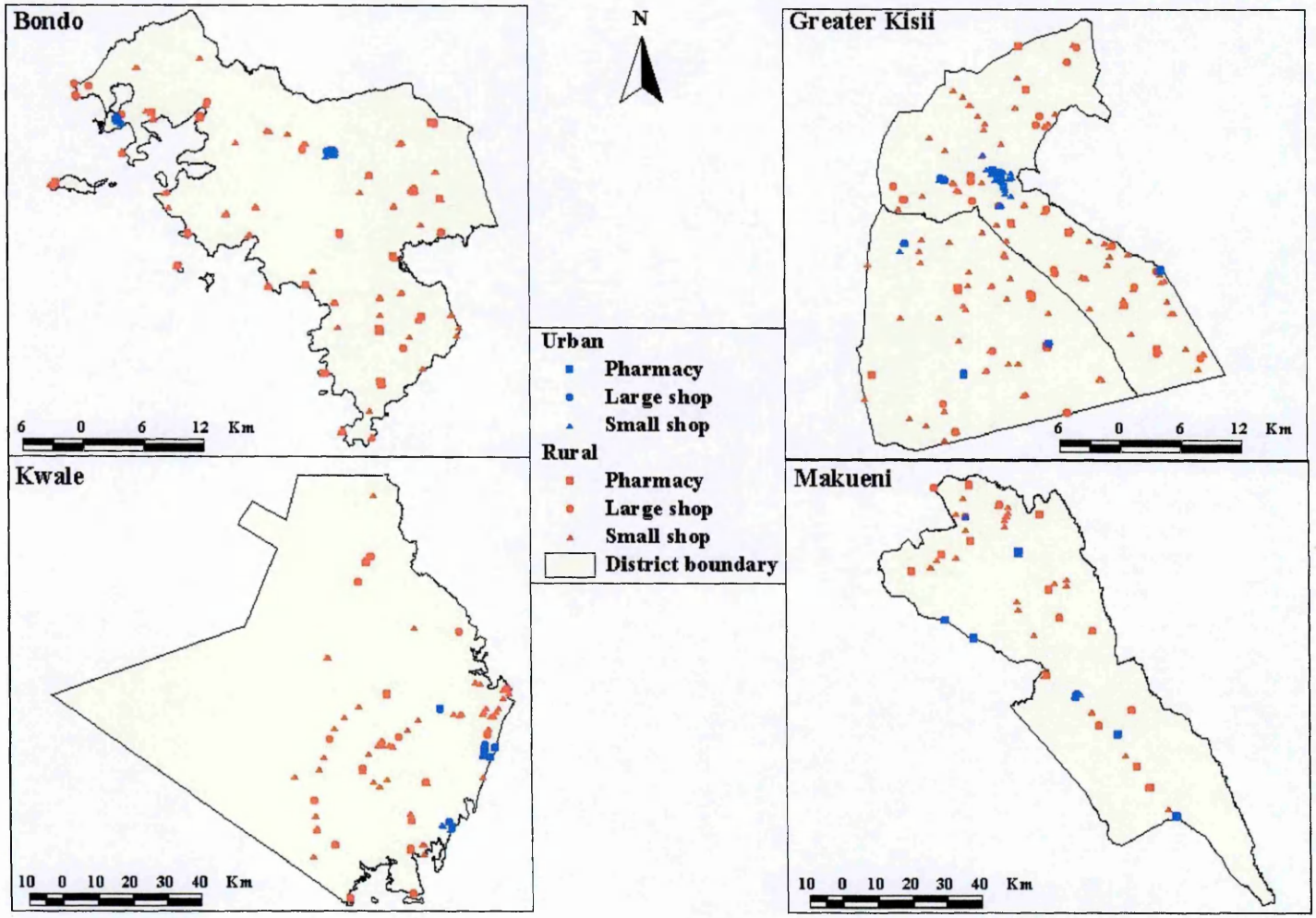


Table 5.2: Characteristics of retail drug outlets and retailers of 876* retail outlets audited in 2002 in four districts of Kenya.

Indicator	Greater Kisii Number of outlets=228	Kwale Number of outlets=210	Bondo Number of outlets=217	Makueni Number of outlets=221	Total Number of outlets=876	P values‡	Post-hoc pairwise comparisons§
Main seller† sex (Males)	128 (51.6%)	147 (70.0%)	76 (35.0%)	92 (41.6%)	443 (50.6%)	<0.001	Kisii-Bondo Kwale-Kisii Kwale-Bondo Kwale-Makueni
Median age (in years) of Main seller (IQR)	33.5 [27.0, 41.0]	27.5 [22.8, 33.0]	28.0 [23.5, 35.0]	28.0 [23.0, 38.0]	30.0 [24.0, 37.0]	<0.001	Kisii-Kwale Kisii-Bondo Kisii-Makueni
Median number of years in school (IQR)	11.0 [8.0, 12.0]	8.0 [8.0, 12.0]	9.0 [8.0, 12.0]	11.0 8.0, 12.0]	10.0 [8.0, 12.0]	0.001	Kisii-Kwale Kisii-Bondo Kwale-Makueni
Median number of years outlet open (IQR)	5.4 [2.3, 10.3]	3.7 [1.5, 7.3]	3.7 [2.2, 6.4]	4.4 [2.0, 8.5]	4.3 [2.0, 8.2]	0.001	Kisii-Kwale Kisii-Bondo
Median number of years (IQR) main seller worked in shop	5.0 [2.0, 10.0]	2.0 [1.0, 4.8]	3.0 [1.0, 5.0]	3.3 [1.2, 7.1]	3.0 [1.2, 6.5]	<0.001	Kisii-Kwale Kisii-Bondo Kwale-Makueni

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

† Main seller defined as person who spent most time in the shop.

‡ Proportions compared using Pearson's Chi-Square. Medians were compared using Kruskal-Wallis test.

§ Dwass-Steel-Crichlow-Fligner or Marascuilo procedure after chi-square.

5.3.2 Preventative antimalarial measures

Table 5.3 shows the relative availability of malaria preventative measures in the districts. The most widely available measures were mosquito coils (sold in 67.9% of outlets) and aerosols (30.5% of outlets). Fifty (5.7%) outlets were found to be retailing branded mosquito nets, with significant differences between the districts (11.0% for Kwale versus <6% in the other districts, χ^2=14.5, df=3, p=0.002). Forty-three (86%) of these outlets were selling Supanet® which is marketed by Population Services International (PSI) under a social marketing programme. Supanet® was available in all the districts at a price range of 200-400 KES. Eight other brands of treated nets were identified: Aggrevo® was available in one outlet in Greater Kisii at a price of 350 KES. Magic marble®, Nettee®, Didisnet® and Dawanet® were sold in Kwale (price range 450 to 550 KES) while Western Kenya net® and Mmbunet® were exclusively found in Bondo (price of 400 KES). Unbranded nets were also sold in outlets in Bondo at a price range of 300 to 600 KES. Apart from Supanet®, the additional brand Globe® was also sold in Makueni.

Forty-eight outlets (5.5%) were retailing insecticides for treating mosquito nets, with price ranging from 30 and 100 KES per net treatment. The majority of the 48 outlets (90%) were retailing PSI's Powertab®. Outlets in Kwale district were almost twice as likely to sell insecticides for treating nets than were outlets in the other districts (11.0% versus <6% in Greater Kisii, Bondo and Makueni, χ^2=16.2, df=3, p=0.001). Three brands of insecticides for treating nets were identified. Powertab® was found in all districts (at 30 to 95 KES), KO Tab® in Kisii, Kwale and Bondo (at 30-86 KES) and Fendona® in Kwale only (at 100 KES). Two outlets (a pharmacy in Bondo and one in Greater Kisii) sold insecticides for indoor residual house spraying and two brands, Flower® and Icon 10WP®, were identified, retailing at KES 204 and 650, respectively.

From an outlet type perspective, a greater proportion of large shops (11.8%, price range 200 to 600 KES) sold treated nets than did pharmacies (5.7%, price range 350 to 550 KES) and small shops (4.2%, price range 200 to 450 KES). Conversely, a greater proportion of pharmacies sold insecticides for treating nets than large or small shops (22.9%, 8.1% and 2.9%, respectively). The price ranges of insecticides for treating nets were 50 to 300 KES in pharmacies, 35 to 86 KES in large shops, and 30 to 90 KES in small shops. Only 18.6% of pharmacies sold mosquito coils compared to 82.0% of large shops and 69.8% of small shops. Aerosols were sold in 34.3% of pharmacies, 58.4%, and 23.1% of large and small shops, respectively. Repellents were sold in 7.1% of pharmacies, 6.2% of large shops, and 2.0% of small shops. Prices and brands of mosquito coils, aerosols, and repellents were not investigated.

Table 5.3: Availability of preventative antimalarial measures in 876* retail outlets audited in 2002 in four districts of Kenya (Greater Kisii n=228, Kwale n=210, Bondo n=217, Makueni n=221). Figures in bracket show proportion of outlets selling a given item. Figures next to individual brands are price or price ranges in KES.

Outlets	Greater Kisii	Kwale	Bondo	Makueni	Total	P values†
Selling Bed nets:	11 (4.8%)	23 (11.0%)	8 (3.7%)	8 (3.6%)	50 (5.7%)	0.002
Supanet®	280-400	200-400	200-400	350	200-400	
Aggrevo®	350	na	na	na	350	
Magic Marble®	na	500	na	na	500	
Nettee®	na	450	na	na	450	
Didisnet®	na	500	na	na	500	
Western Kenya Net®	na	na	400	na	400	
Mmbunet®	na	na	400	na	400	
Globe®	na	na	na	400	400	
Dawanet®	na	550	na	na	550	
Unbranded net	na	na	300-600	na	300-600	
Selling Insecticides for bed nets:	9 (3.9%)	23 (11.0%)	7 (3.2%)	9 (4.1%)	48 (5.5%)	0.001
Powertab®	50-95	30-95	50-86	50-90	30-95	
KO tab®	50	30-50	50-86	na	30-86	
Fendona®	na	100	na	na	100	
Selling Insecticides for indoor residual spraying:	1	0	1 (0.5%)	0	1 (0.1%)	0.385
Icon 10WP®	650	na	na	na	650	
Flower®	na	na	204	na	204	
Selling Mosquito coils	125 (54.8%)	174 (82.9%)	140 (64.5%)	156 (70.6%)	595 (67.9%)	<0.001
Selling Aerosols	70 (30.7%)	90 (42.9%)	48 (22.1%)	59 (26.7%)	267 (30.5%)	<0.001
Selling mosquito repellents	8 (3.5%)	6 (2.9%)	4 (1.8%)	10 (4.5%)	28 (3.2%)	0.441

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.
† Proportions compared using Pearson's Chi-Square.

5.3.3 General drug stocks

Retailers were asked a series of close-ended questions on common drugs in stock, i.e. if they stocked AP, anti-diarrhoeal (AD), anticough (AC) and antihelminthic (AH) drugs. Table 5.4 shows the results to these questions. There were differences in the proportion of outlets selling the various drug classes between the districts, except in the case of AP drugs (χ^2=3.96, df=3, p=0.266). Nearly all outlets (>97% of outlets) sold AP drugs in all districts.

Table 5.4: Stocks of common drugs available in 876* retail outlets in four districts in Kenya in 2002 (AP=Antipyretic, AD=Antidiarrhoeial, AC=Anticough, AH=Antihelminthic)

Outlets selling	Greater Kisii	Kwale	Bondo	Makueni	Total
AP drugs	225 (98.7)	209 (99.5)	211 (97.2)	218 (98.6)	863 (98.5)
AD drugs	113 (49.6)	166 (79.0)	114 (52.5)	152 (68.8)	545 (62.2)
AC drugs	151 (66.2)	196 (93.3)	168 (77.4)	168 (76.0)	683 (78.0)
AH drugs	85 (37.3)	124 (59.0)	62 (28.6)	85 (38.5)	356 (40.6)

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

5.3.4 Range of AM drugs at national and district levels

Table 5.5 shows the results of the national audit of AM drugs in circulation, their registration status with the PPB, whether locally manufactured or imported and their associated prices. From the national audit, 218 AM products (oral) were identified, 135 (61.9%) of which were registered with the PPB. All artemisinin (ART) and mefloquine (MEF) tablets were registered while none of the ART suspensions or halofantrine (HAL) products were registered. Almost half of first and second-line AM drugs remained unregistered; of 65 SP products identified 34 (52.3%) were registered with the PPB whilst for AQ, 51.5% of products were registered with the PPB.

Overestimation of products at the national level could have occurred because only first time product registration was considered. This means that products which were registered but never marketed for commercial reasons or those which were initially marketed but later withdrawn by the PPB (for regulatory reasons) or the manufacturer or dealer (for commercial reasons) could potentially have been included in the list. Data needed to clear such doubts were unavailable from the PPB.

Table 5.5: National audit of oral anti-malarial drugs available on the Kenyan market in 2002

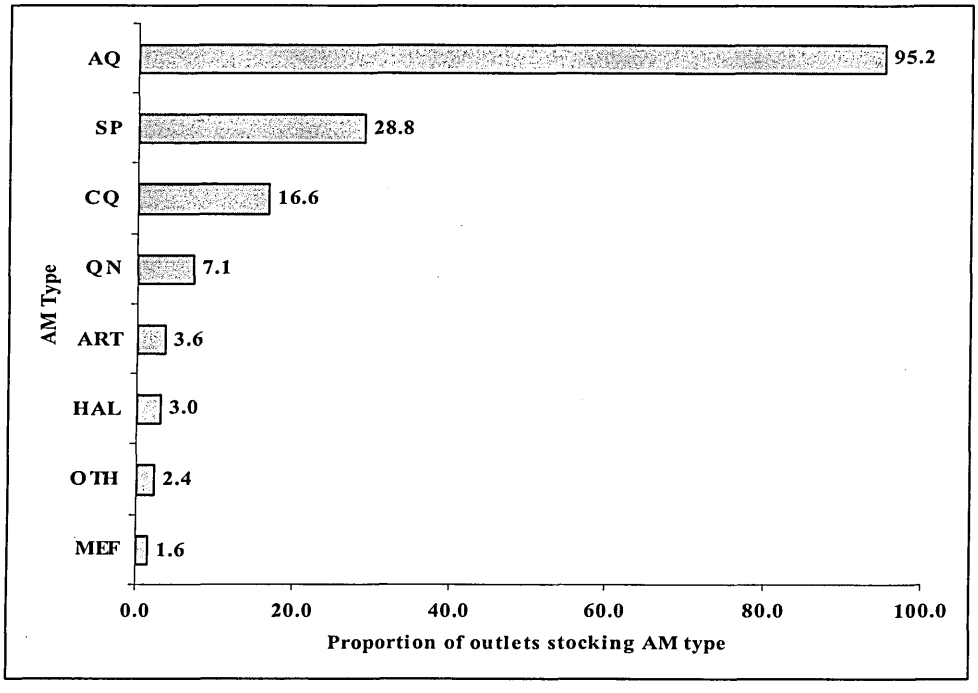
Generic Name	# Brands identified (registered)*	# Brands manufactured in Kenya (registered)	# Brands imported into Kenya (registered)	Median (IQR) price (KES) of Rx course†	Median (IQR) price (USD) of Rx course†
SP tablets	49 (29)	11 (7)	38 (22)	15.0 [9.9, 25.5]	0.19 [0.13, 0.32]
SP suspensions and drops‡	16 (5)	11 (3)	5 (2)	30.6 [22.3, 41.6]	0.39 [0.28, 0.53]
AQ tablets	22 (12)	12 (7)	10 (5)	13.5 [10.8, 43.2]	0.17 [0.14, 0.55]
AQ suspensions	11 (5)	9 (5)	2 (2)	21.7 [12.0, 38.3]	0.28 [0.15, 0.49]
CQ tablets	43 (33)	17 (10)	26 (23)	7.4 [6.0, 15.3]	0.09 [0.08, 0.19]
CQ syrups	22 (10)	17 (6)	5 (4)	3.7 [2.5, 23.7]	0.05 [0.03, 0.30]
QN tablets	25 (19)	9 (7)	16 (12)	215.5 [189.0, 248.9]	2.73 [2.40, 3.16]
QN drops and mixtures	3 (1)	3 (1)	0	176.4 [147.0, 236.3]	2.24 [1.87, 3.00]
ART tabs	11 (11)	1 (1)	10 (10)	420.0 [327.9, 438.1]	5.34 [4.16, 5.56]
ART suspensions	1 (0)	0	1 (0)	304.5 [304.5, 304.5]	3.86 [3.86, 3.86]
MEF tablets	4 (4)	0	4 (4)	397.5 [301.5, 751.1]	5.04 [3.83, 9.53]
HAL tablets	1 (0)	0	1 (0)	627.0 [627.0, 627.0]	7.96 [7.96, 7.96]
HAL suspensions	1 (0)	0	1 (0)	222.9 [222.9, 222.9]	2.83 [2.83, 2.83]

* Registration: only **first time** registration was considered; withdrawals, re-registration after expiry of the mandatory 5-year period or lack thereof was not considered. Registration period covers up to and including May 31 2002.
† For packaged commodities, the calculations were derived per tablet and per recommended dose for adults. Where possible, large, bulk packaging was selected for individual suppliers to provide the cheapest values.
‡ Liquid dosage forms (suspensions, syrups, mixtures and paediatric drops) were all priced per dosage per child aged 1-5 years – not adult treatment courses. The mean dose per product was calculated as the mid-point between the DOMC recommended dose for a 1 year old (lower limit of 10kg) and a 5 year old (upper limit of 18kg)

Figure 5.2 shows the stocking frequencies of the various AM drug classes encountered in the districts. AQ (the second-line drug at the time) was stocked by over 95% of retail outlets, followed by SP (the first-line drug), which was stocked by only 29% of retail outlets. CQ, which had been replaced by SP in 1998 as first-line drug was still available in retail outlets (17%). Other AM drugs were available in less than 10% of retail outlets.

Tables 5.6 to 5.10 present further details of the district level data in terms of the specific products encountered, their registration status and their relative stocking frequencies per retail category. Overall, AQ, SP, and CQ tablets were available in all retail categories in all the districts. AQ, SP and CQ syrups were available in all pharmacies and some general retail shops, but artemisinin (ART) products, halofantrine (HAL) and mefloquine (MEF) were exclusively sold in pharmacies.

Figure 5.2: Stocking frequencies of AM drugs in retail outlets audited in 2002



For AQ tablets, 13 brands were identified of which six (46.2%) were registered with the PPB. Three brands (which were not registered) were only encountered in the districts and were not recorded during the national audit. These were Amowin® in Greater Kisii and Vanida® and Maratab® in Makueni. Malaratab® was the most widely stocked AQ tablet, found in 87.9% of outlets. Twelve brands of AQ syrup were encountered, 5 (41.7%) registered with the PPB; the most widely stocked being Amobin®, found in 4.3% of retail outlets.

Thirty brands of SP tablets were encountered in the districts, the two most widely stocked being Falcidin® (stocked by 19.9% of outlets) and Fansidar® (8.8%). Sixteen brands (53.3%) were registered with the PPB. Zentakelfin®, Sudorin® and Lansidar® (all unregistered) were available in some district level pharmacies and not recorded during the national audit. Fifteen brands of SP suspensions were also encountered. Of these, only Falcidin® and Kelfalin® were registered with the PPB. Pyralfin® syrup was the most widely stocked (found in 2.5% of outlets) followed by Falcidin® syrup (2.1%). The number of brands and registration status of the other AM classes were as follows: CQ tablets (12, 41.7% registered), CQ syrups (9, 44.4% registered), QN tablets (3, 66.7% registered), QN syrups (4, 25% registered), MEF tablets (4, all registered), HAL tablets (1, not registered), HAL syrup (1, not registered), ART tablets and combinations (7, all registered), ART syrups (2, none registered), others (2, all registered). Products identified in the districts, but not recorded during the national audit were: C-quin® and SK-quine® tablets (CQ), Flaci-quin® tablets, Quinaquin® and Quinamor® syrups (QN), and Artesiane® syrup (ART). All of these remained unregistered with the PPB.

Table 5.6: Range of AQ products available in 876* retail outlets in four districts in Kenya in 2002 expressed as percent outlet type selling given product. Asterix indicates products not registered with PPB up to May 31, 2002.

	Pharmacies	Large shops	Small shops	Total
AQ tablets				
Malaratab® .	71.4%	89.4%	89.3%	87.9%
Betaquine®*	21.4%	16.1%	15.2%	15.9%
Emoquin®*	11.4%	3.7%	3.4%	4.1%
Alphaquine®*	1.4%	5.6%	3.6%	3.8%
Laeoquin®	2.9%	1.9%	2.6%	2.5%
Camoquin®	22.9%	-	-	1.8%
AQ unspecified	8.6%	-	-	0.7%
Kamoc®*	8.6%	-	-	0.7%
Uniquin®	7.1%	-	0.2%	0.7%
Amobin®	5.7%	-	-	0.5%
Amowin®*	4.3%	-	-	0.3%
Diaquin®	1.4%	0.6%	0.2%	0.3%
Vanida®*	-	-	0.3%	0.2%
Maratab®*	1.4%	-	-	0.1%
AQ suspensions				
Amobin®*	51.4%	0.6%	0.2%	4.3%
Malaramed®*	35.7%	0.6%	-	3.0%
Malaratab®	34.3%	-	0.2%	2.9%
Falciquin®*	22.9%	-	0.2%	1.9%
Kamoc®*	22.9%	-	0.2%	1.9%
Malarabit®*	17.1%	-	-	1.4%
Emoquin®	12.9%	-	-	1.0%
Camoquin®*	11.4%	-	-	0.9%
Uniquin®	11.4%	-	-	0.9%
Amoquin®*	4.3%	-	0.2%	0.5%
Laeoquin®	5.7%	-	-	0.5%
Diaquin®	1.4%	-	-	0.1%

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

Table 5.7: Range of SP tablet products available in 876* retail outlets in four districts in Kenya in 2002 expressed as percent outlet type selling given product. Asterix indicates products not registered with PPB up to May 31, 2002.

	Pharmacies	Large shops	Small shops	Total
Falcidin®	42.9%	27.3%	15.5%	19.9%
Fansidar®	81.4%	5.0%	1.9%	8.8%
Orodar®	42.9%	6.2%	3.4%	7.1%
Metakelfin®	74.3%	1.2%	0.8%	6.7%
Pyralfin®*	25.7%	-	-	2.1%
Malodar®	12.9%	1.2%	0.9%	1.9%
Laefin®*	17.1%	-	0.2%	1.5%
Malareich®	11.4%	-	0.8%	1.5%
Amalar®	14.3%	-	0.3%	1.4%
Malidar®*	12.9%	-	-	1.0%
Metfin®*	11.4%	-	-	0.9%
Nopyrin®*	8.6%	0.6%	0.2%	0.9%
Malostat®	10.0%	-	-	0.8%
Zentakelfin®*	8.6%	-	0.2%	0.8%
Fanlar®	2.9%	-	0.5%	0.6%
Intadoxin®	5.7%	0.6%	-	0.6%
UB-Gomal®	5.7%	-	0.2%	0.6%
Malastin®	5.7%	-	-	0.5%
Rimodar®*	5.7%	-	-	0.5%
Lansidar®*	4.3%	-	-	0.3%
Methomine®	2.9%	-	0.2%	0.3%
SP unspecified	4.3%	-	-	0.3%
Unidar®*	4.3%	-	-	0.3%
Viparum®	2.9%	-	0.2%	0.3%
Falcigo®*	2.9%	-	-	0.2%
Fansmax®	2.9%	-	-	0.2%
Maladar®	-	0.6%	0.2%	0.2%
Metakin®*	2.9%	-	-	0.2%
Methomine-S®*	2.9%	-	-	0.2%
Laridox®*	1.4%	-	-	0.1%
Sudorin®*	1.4%	-	-	0.1%

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

Table 5.8: Range of SP suspension products available in 876* retail outlets in four districts in Kenya in 2002 expressed as percent outlet type selling given product. Asterix indicates products not registered with PPB up to May 31, 2002.

	Pharmacies	Large shops	Small shops	Total
Pyralfin®*	31.4%	-	-	2.5%
Falcidin®	24.3%	-	0.2%	2.1%
Intadoxin®*	20.0%	-	0.2%	1.7%
Falcigo®*	18.6%	-	-	1.5%
Medifan®*	14.3%	-	0.2%	1.3%
Orodar®*	11.4%	-	-	0.9%
Falcimax®*	10.0%	-	-	0.8%
Kelfalin®	8.6%	-	-	0.7%
Lansidar®*	8.6%	-	-	0.7%
Malidar®*	8.6%	-	-	0.7%
Nopyrin®*	5.7%	-	-	0.5%
Laefin®*	4.3%	-	-	0.3%
Unidar®*	4.3%	-	-	0.3%
Fansmax®*	1.4%	-	-	0.1%
Viparum®*	1.4%	-	-	0.1%

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

Table 5.9: Range of CQ products available in 876* retail outlets in four districts in Kenya in 2002 expressed as percent outlet type selling given product. Asterix indicates products not registered with PPB up to May 31, 2002.

	Pharmacies	Large shops	Small shops	Total
CQ tablets				
Dawaquin®	4.3%	5.6%	4.2%	4.5%
CQ unspecified	25.7%	1.2%	1.9%	3.7%
Malaraquin®*	-	3.1%	2.9%	2.7%
Homaquin®	2.9%	1.2%	1.9%	1.8%
Oroquin®	5.7%	0.6%	0.9%	1.3%
Intaclor®*	1.4%	-	0.3%	0.3%
Cosmoquin®	-	0.6%	-	0.1%
C-Quin®*	1.4%	-	-	0.1%
Maxaquin®*	1.4%	-	-	0.1%
Nivaquine®	-	-	0.2%	0.1%
Novaclor®*	1.4%	-	-	0.1%
Oraclor®*	1.4%	-	-	0.1%
Rohoquin®*	1.4%	-	-	0.1%
CQ suspensions				
Mediquine®	17.1%	-	-	1.4%
Phinaquine®	15.7%	-	-	1.3%
Oroquin®*	12.9%	-	-	1.0%
Novaclor®*	8.6%	-	-	0.7%
Bioquin®*	2.9%	-	-	0.2%
Gestaquin®	1.4%	-	-	0.1%
Intaclor®	1.4%	-	-	0.1%
Rohoquin-P®*	1.4%	-	-	0.1%
SK-Quine®*	1.4%	-	-	0.1%

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

Table 5.10: Range of quinine (QN), halofantrine (HAL), mefloquine (MEF), artemisinin (ART) and proguanil (PRO) products available in 876* retail outlets in four districts in Kenya in 2002 expressed as percent outlet type selling given product. Asterix indicates products not registered with PPB up to May 31, 2002.

	Pharmacies	Large shops	Small shops	Total
QN tablets				
QN unspecified	38.6	-	-	3.1
Quinitab®	12.9	-	-	1.0
Flaci-Quin®*	1.4	-	-	0.1
Kwinil®	1.4	-	-	0.1
QN suspensions				
QN unspecified	48.6	0.6	0.2	4.1
Quinaquin®*	14.3	0.6	-	1.3
Quinamor®*	12.9	-	-	1.0
Quinitab®	8.6	-	-	0.7
Quinidril®*	7.1	-	-	0.6
HAL tablets				
Halfan®	31.4	-	-	2.5
HAL suspensions				
Halfan®	25.7	-	-	2.1
MEF tablets				
Mephaquin®	20.0	-	-	1.6
Lariam®	2.9	-	-	0.2
Mefliam®	1.4	-	-	0.1
Meflotas®	1.4	-	-	0.1
ART tablets				
Artenam®	22.9	-	-	1.8
Cotecxin®	21.4	-	-	1.7
Arsumax®	20.0	-	-	1.6
Arinate®	14.3	-	-	1.1
Coartem®	11.4	-	-	0.9
Larither®	7.1	-	-	0.6
Alaxin®	1.4	-	-	0.1
ART suspensions				
Cotecxin®*	27.1	-	-	2.2
Artesiane®*	7.1	-	-	0.6
PRO tablets				
Paludrine®	25.7	-	-	2.1
PRO unspecified	17.1	-	-	1.4

* Four shops in Bondo were excluded from analysis. They remained closed even after three repeated visits.

5.3.5 Prices of products at national and district levels

The registration status of the products encountered during the national audit has been discussed in Section 5.3.4. For product prices, standardised dose regimens were used to enable comparisons between the AM classes. AQ, CQ, SP and QN doses were based on the malaria standard treatment guidelines of the DOMC of the MoH (DOMC, 1998). For all other AM drugs (which are not the subject of DOMC guidelines), The East African Pharmaceutical Loci, a regional formulary for healthcare professionals, was used (Kimotho *et al.*, 2002). Where possible, large bulk packaging was selected per supplier to provide the cheapest national or source values to enable a description of price differentials between national and district levels to be established (albeit with limited success).

Overall, at the national level, CQ syrup (for children less than five years) was the cheapest form of therapy for uncomplicated malaria at a median price of 3.7 KES (IQR 2.5, 23.7) while HAL tablets were the most expensive at 627.0 KES (IQR 627.0, 627.0). An adult dose of SP was priced at 15.0 KES (IQR 9.9, 25.5) while a standard dose for a paediatric patient on SP suspensions was priced nearly twice as much. AQ tablet and suspension prices were comparable to SP (13.5 KES for an adult dose and 21.7 KES for a paediatric dose, respectively). The price range for QN, MEF, and ART products was 176.4 to 420 KES, at least 10 times that of SP tablets (Table 5.5).

Price data for the districts were treated in a similar manner and are summarised in Table 5.11. Further, Figures 5.3 and 5.4 show prices of adult and paediatric doses of SP and AQ (first- and second-line, respectively at the time of the surveys), CQ (first-line AM till 1998, but still in circulation) and the ART derivatives. Taken together, a number of observations emerge. First, in both pharmacies and shops, CQ remained the cheapest therapy among adults (price range 8.3 to 37.5 KES) and children (13.8 to 20.6 KES) for treatment of

uncomplicated falciparum malaria, followed by SP and AQ. The price of SP tablets ranged from 20 to 40 KES in the districts for an adult treatment course, representing between a 33% and 167% mark-up when compared to the cheapest prices obtained from manufacturers at factory gates. A similar adult course of AQ tablets was 60 KES compared to the cheapest prices at factory gates of 14 KES. The price ranges for SP and AQ suspensions were 26.3 to 39.4 KES and 32.2 to 43.8 KES, respectively. In contrast, QN, HAL, MEF, and ART remained relatively expensive. In this latter group, QN syrup was the least expensive, ranging from 210 to 315 KES per paediatric treatment course. ART tablets and combinations were priced at 560 to 583.3 while their suspensions (for paediatric treatment courses) ranged from 367.5 to 411.3 KES equivalent to about 5 US dollars at the exchange rate of the survey period (Central Bank of Kenya (CBK) exchange rate for last working day of June 2002 was 78.8 KES to the USD).

Table 5.15 shows that there were significant differences in the price of an adult dose of AQ between the districts (Kruskal-Wallis=11.6, df=3, p=0.009) with Bondo being significantly different from both Kwale and Makueni. There were also significant differences in the prices of CQ (Kruskal-Wallis=26.4, df=3, p<0.001) and QN (Kruskal-Wallis=9.8, df=3, p=0.021) between the districts. For CQ, Greater Kisii was found to be significantly different from Kwale and Bondo, and Kwale different from Bondo, and Bondo from Makueni. For QN, the only difference was between Greater Kisii and Kwale. For the paediatric formulations, there were significant differences in the price of AQ between the districts (Kruskal-Wallis=18.6, df=3, p<0.001) and also in the prices of QN (Kruskal-Wallis=8.2, df=3, p=0.042). For AQ, the differences were between Makueni and Kwale, and Makueni and Bondo. For QN, only Greater Kisii was significantly different from Bondo.

A comparison of the prices of adult doses of AQ, SP and CQ between pharmacies, large shops and small shops reveals that there were differences in the prices of AQ between large and small shops (Kruskal-Wallis=18.3, df=2, p<0.001). For SP and CQ, there were differences between pharmacies and large shops and between pharmacies and small shops (Kruskal-Wallis=38.1, df=2, p<0.001 and Kruskal-Wallis=53.8, df=2, p<0.001 for SP and CQ, respectively). There were no large shops stocking SP suspensions. A comparison of SP suspensions between pharmacies and small shops reveals no significant difference (Kruskal-Wallis=0.9, df=1, p=0.347). There were no large or small shops with CQ syrups. All retail outlet categories stocked AQ syrups and the difference in paediatric prices between the retail outlet types was not significant (Kruskal-Wallis=2.0, df=2, p=0.373).

There were no significant differences in the adult prices of AQ between rural and urban outlets (Kruskal-Wallis=2.8, df=1, p=0.093). Likewise, there were no significant differences in the adult prices of SP (Kruskal-Wallis=0.02, df=1, p=0.879), CQ (Kruskal-Wallis=1.2, df=1, p=0.282) QN (Kruskal-Wallis=0.9, df=1, p=0.348), HAL (Kruskal-Wallis=1.8, df=1, p=0.178), MEF (Kruskal-Wallis<0.001, df=1, p>0.999), and ART (Kruskal-Wallis=0.3, df=1, p=591) between rural and urban settings. For paediatric formulations, HAL was only found in urban settings; therefore, there was no rural comparator. There were no significant differences between paediatric doses of AQ in rural and urban settings (Kruskal-Wallis=0.9, df=1, p=0.353) or that of other AM drugs in these settings: SP (Kruskal-Wallis=0.9, df=1, p=0.339); CQ (Kruskal-Wallis=0.1, df=1, p=0.707); QN (Kruskal-Wallis=0.7, df=1, p=0.412), and ART (Kruskal-Wallis=1.5, df=1, p=0.214).

Table 5.11: Median prices in KES [interquartile ranges (IQR)] of treatment courses of AM drug classes available at district level outlets in 2002 by district and rural/urban outlets

	Greater Kisii	Kwale	Bondo	Makueni	Rural	Urban	Total
SP Tablets	30.0 [20.0, 60.0]	30.0 [20.0, 40.0]	30.0 [20.0, 60.0]	25.0 [20.0, 53.3]	30.0 [20.0, 45.0]	30.0 [20.0, 60.0]	30.0 [20.0, 51.3]
SP Syrups	35.0 [32.8, 41.6]	39.4 [29.2, 43.8]	39.4 [32.8, 43.8]	39.4 [35.0, 43.8]	39.4 [35.0, 43.8]	35.0 [31.7, 43.8]	35.0 [35.0, 43.8]
AQ Tablets	60.0 [60.0, 60.0]	60.0 [45.0, 60.0]	60.0 [60.0, 75.0]	60.0 [60.0, 60.0]	60.0 [60.0, 60.0]	60.0 [60.0, 60.0]	60.0 [60.0, 60.0]
AQ Syrups	43.8 [32.8, 43.8]	43.8 [36.5, 58.3]	43.8 [32.8, 51.0]	36.5 [25.5, 43.8]	43.8 [35.4, 47.4]	36.5 [29.2, 49.2]	40.1 [31.0, 47.4]
CQ Tablets	35.0 [20.0, 35.0]	35.0 [30.0, 40.0]	10.0 [8.3, 35.0]	35.0 [15.6, 35.0]	35.0 [23.8, 35.0]	35.0 [10.0, 35.0]	35.0 [20.0, 35.0]
CQ Syrups	20.6 [20.6, 30.9]	25.2 [22.9, 27.5]	13.8 [4.1, 20.6]	20.6 [10.2, 25.8]	17.2 [5.0, 24.1]	20.6 [4.1, 24.8]	20.6 [4.5, 24.1]
QN Tablets	252.0 [189.0, 267.8]	378.0 [315.0, 409.5]	315.0 [252.0, 315.0]	252.0 [189.0, 252.0]	283.5 [252.0, 362.3]	252.0 [189.0, 315.0]	252.0 [189.0, 315.0]
QN Syrups	262.5 [237.7, 315.0]	315.0 [252.0, 378.0]	315.0 [295.3, 367.5]	315.0 [238.0, 315.0]	315.0 [262.5, 367.5]	315.0 [252.0, 315.0]	315.0 [257.3, 315.0]
ART tablets	500.0 [450.0, 583.3]	560.0 [495.0, 623.0]	595.0 [490.0, 700.0]	583.3 [520.8, 595.8]	525.0 [490.0, 560.0]	560.0 [484.2, 630.0]	560.0 [484.2, 627.1]
ART suspensions	367.5 [302.7, 393.8]	411.3 [324.6, 428.8]	389.4 [287.8, 393.8]	371.9 [350.0, 393.8]	415.6 [415.6, 415.6]	393.8 [350.0, 402.5]	393.8 [350.0, 404.5]
MEF tablets	580.0 [476.5, 750.0]	600.0 [600.0, 895.0]	590.0 [535.0, 607.5]	-	600.0 [600.0, 600.0]	600.0 [575.0, 630.0]	600.0 [577.5, 620.0]
HAL tablets	750.0 [610.0, 788.0]	833.0 [762.5, 847.5]	780.0 [747.5, 781.0]	675.0 [650.0, 700.0]	840.0 [840.0, 840.0]	780.0 [720.0, 800.0]	780.0 [730.0, 807.5]
HAL suspension	280.0 [243.6, 281.1]	294.0 [270.2, 327.6]	274.4 [264.3, 288.4]	238.0 [224.0, 252.0]	-	280.0 [252.0, 292.6]	280.0 [252.0, 292.6]

Figure 5.3: Prices of adult doses of AQ, SP, CQ and ART in Kenya Shillings (KES) in four districts of Kenya. Greater Kisii (red), Kwale (green), Bondo (blue) and Makueni (purple). Central Bank of Kenya mean exchange rate to the US dollar in June was 78.8 KES (last working day of the month selected, http://www.centralbank.go.ke, accessed 07/12/04).

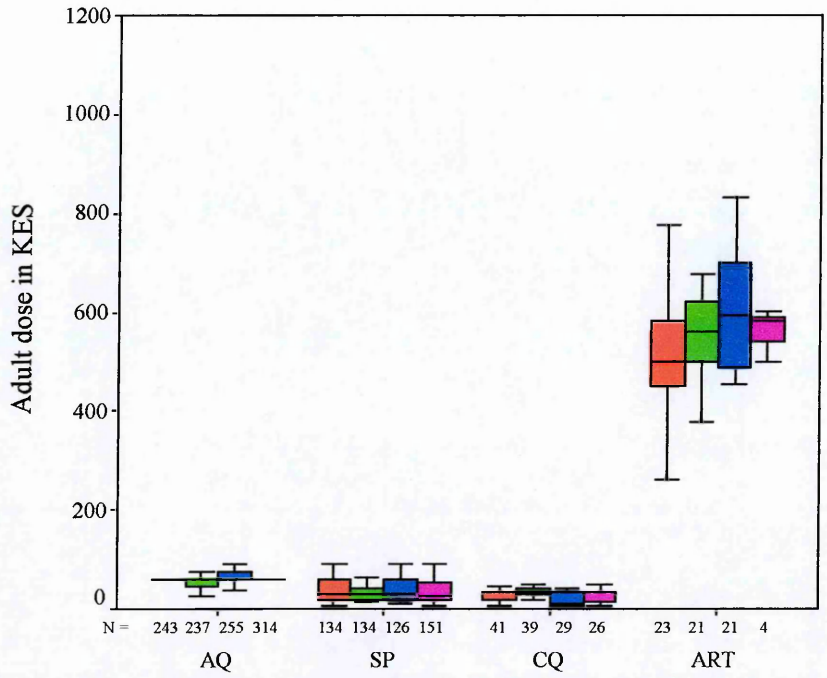


Figure 5.4: Prices of paediatric doses of AQ, SP, CQ and ART in Kenya Shillings (KES) in four districts of Kenya. Greater Kisii (red), Kwale (green), Bondo (blue), and Makueni (purple). Central Bank of Kenya mean exchange rate to the US dollar in June was 78.8 KES (last working day of the month selected, http://www.centralbank.go.ke, accessed 07/12/04).

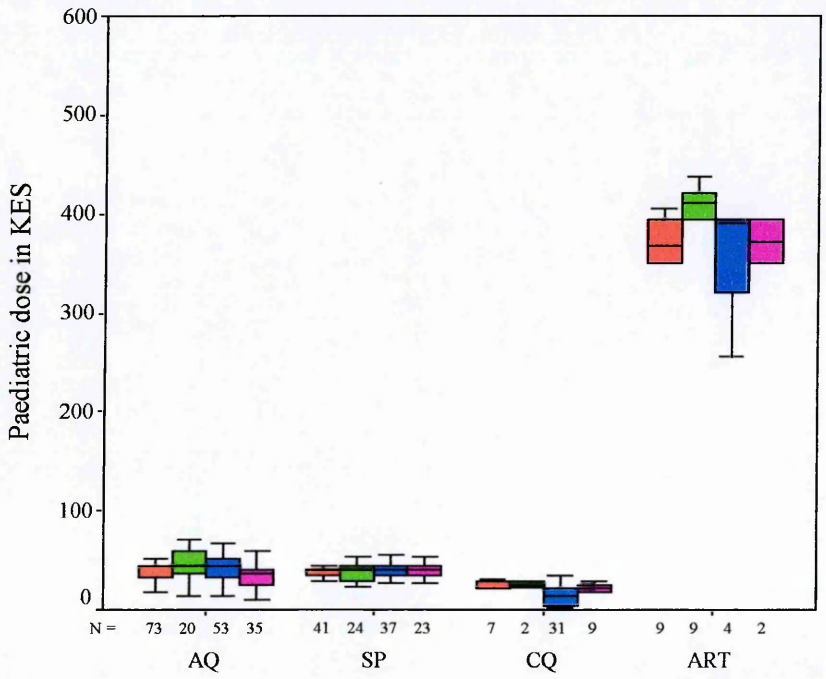
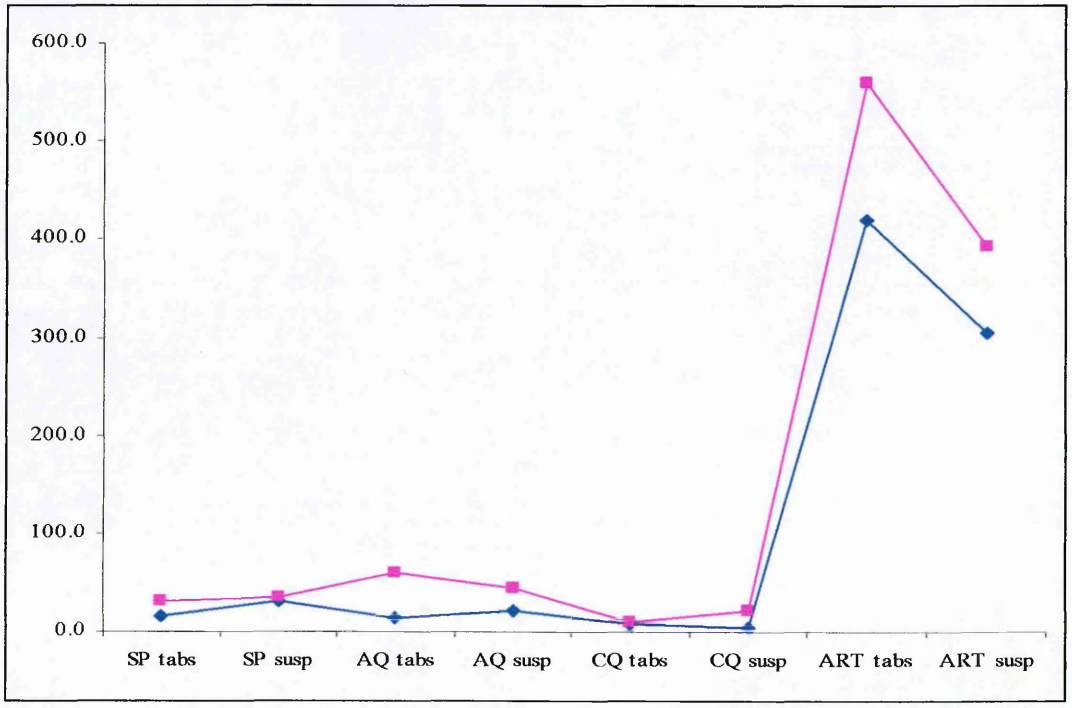


Figure 5.5 shows median prices in KES of AQ, SP, CQ and ART tablets and suspensions against their cheapest national prices to demonstrate mark-ups. Because large shops and small shops did not stock all these products and their tablet and suspensions as well, they were excluded from this part of the analysis. There was no consistency in the mark-ups. The smallest mark-up was on SP suspensions at 14% and the highest on CQ suspensions at four and half times the price of the cheapest national source. Mark-ups on CQ tablets, ART tablets and ART suspensions were 35, 33, and 29%, respectively. AQ tablets in retail pharmacies were priced almost three times the cheapest national price (344%), while SP tablets and AQ suspensions were priced twice the national price (100 and 101%, respectively), suggesting a very high variability in regulations for different products in the retail pharmacy sector.

Figure 5.5: Median prices (KES) of AQ, SP, CQ and ART drugs in 70 retail pharmacies in Kenya (pink) against the cheapest national prices (blue) for the same category. The gap between the two lines represents the mark-up from factory gates.



5.3.6 Sources of wholesale AM drugs to retailers

For pharmacies, because of the wide range of products, it was not possible to ask the wholesale source of individual products. Therefore, respondents were asked the primary wholesale source of AM drugs in stock at the time. For large and small *dukas*, the source of each product audited was inquired. For the analysis in this section, the wholesale source of most products in stock was adopted as the primary source of AM drugs for each outlet. Drug sources thus defined were classified into eight classes as shown in Table 5.12. Results demonstrate that overall pharmacies obtained their AM drugs mostly from pharmaceutical wholesalers outside the districts (67.1%). Large shops obtained their drugs from general wholesalers outside the districts (39.8%) or inside the district 34.8%. Most small shops (45.3%) obtained AM drugs from general wholesalers within the districts. A substantial proportion of small shops (23.3%) also obtained their AM drugs from general wholesalers outside the districts. Mobile or itinerant vendors supplied a good number of small shops (14.0%) and large shops (7.5%), but not pharmacies.

Differences were observed in terms of drug supply between districts. The majority of pharmacies (75.0%), large shops (70.8%), and small shops (69.4%) in Greater Kisii sourced AM drugs from within the district. In contrast, all pharmacies in Kwale sourced AM drugs from outside the district (mostly Mombasa), as did most large shops (75.0%) and a good proportion of small shops (42.5%). Also most pharmacies in Bondo and Makueni (90.0% and 80.0%, respectively) sourced AM drugs from neighbouring districts (Kisumu for Bondo and Machakos and Nairobi for Makueni). Most small shops in Makueni (52.8%) obtained AM drugs from within the district while half of the large shops did so from neighbouring districts. Company drug representatives and direct purchases from pharmaceutical companies did not represent main sources of AM drugs for any of the districts.

Table 5.12: Primary wholesale sources of AM products to 876* retailers in the four study districts.

	Greater Kisii			Kwale			Bondo			Makueni			Totals		
	Pharmacies	**Large Shops**	**Small Shops**	**Pharmacies**	**Large Shops**	**Small Shops**	**Pharmacies**	**Large Shops**	**Small Shops**	**Pharmacies**	**Large Shops**	**Small Shops**	**Pharmacies**	**Large Shops**	**Small Shops**
Mobile vendors	0	0	2 (1.3%)	0	3 (7.5%)	16 (10.0%)	0	4 (12.1%)	35 (21.3%)	0	5 (12.5%)	37 (23.0%)	0	12 (7.5%)	90 (14.0%)
General wholesalers-within district	0	34 (70.8%)	111 (69.4%)	0	3 (7.5%)	55 (34.4%)	0	8 (24.2%)	41 (25.0%)	0	11 (27.5%)	85 (52.8%)	0	56 (34.8%)	292 (45.3%)
General wholesaler-outside district	1 (5.0%)	0	1 (0.6%)	0	30 (75.0%)	68 (42.5%)	0	14 (42.4%)	51 (31.1%)	1 (5.0%)	20 (50.0%)	30 (18.6%)	2 (2.9%)	64 (39.8%)	150 (23.3%)
Pharmaceutical wholesaler-within district	15 (75.0%)	11 (22.9%)	44 (27.5%)	0	0	0	1 (5.0%)	0	5 (3.0%)	1 (5.0%)	0	2 (1.2%)	17 (24.3%)	11 (6.8%)	51 (7.9%)
Pharmaceutical wholesaler-outside district	3 (15.0%)	0	0	10 (100.0%)	1 (2.5%)	1 (0.6%)	18 (90.0%)	2 (6.1%)	8 (4.9%)	16 (80.0%)	0	4 (2.5%)	47 (67.1%)	3 (1.9%)	13 (2.0%)
Pharmaceutical company	1 (5.0%)	3 (6.3%)	0	0	0	0	0	0	0	1 (5.0%)	0	0	2 (2.9%)	3 (1.9%)	0
Drug representative	0	0	0	0	2 (5.0%)	4 (2.5%)	0	1 (3.0%)	0	0	4 (10.0%)	1 (0.6%)	0	7 (4.3%)	5 (0.8%)
Unknown	0	0	2 (1.3%)	0	1 (2.5%)	16 (10.0%)	1 (5.0%)	4 (12.1%)	24 (14.6%)	1 (5.0%)	0	2 (1.2%)	2 (2.9%)	5 (3.1%)	44 (6.8%)

* Four small retailers were excluded from analysis since they remained closed even after three repeated visits.

5.3.7 Advertising and Information, Education and Communication (IEC)

Official MoH IEC materials were observed in the outlets together with branded advertising for malaria drugs, AP drugs, and malaria preventative measures (Table 5.13). Adverts were classified into two types: wall paintings (for example Figure 5.6) which covered the façade or all of the building in which the outlet was housed and other adverts such as branded light boxes or promotional posters (for example Figure 5.7). Results demonstrated that wall adverts were very rare; less than 1% of all outlets had them with no significant differences between the districts (χ^2=3.82, df=3, p=0.281). In contrast, almost a third of all outlets (34.9%) had other promotional materials for malaria within the retail outlets, with no significant differences between the districts (χ^2=4.86, df=3, p=0.182). There were significant differences between the districts in the presence of DOMC posters (χ^2=8.76, df=3, p=0.033) and leaflets (χ^2=12.9, df=3, p=0.005), although these were very rarely available (<3% of outlets).

Retailers were also asked if their outlet had been visited in the preceding 12 months by MoH personnel for the purposes of inspection. Overall, 41.6% of outlets had been inspected, with differences between the districts ((χ^2=78.8, df=3, p<0.001). Makueni and Bondo districts had higher inspection rates (46.6 and 63.6%, respectively) while less than 30% of outlets in Kwale and Greater Kisii had been inspected.

Table 5.13: Presence of advertising and IEC materials for malaria in 876 retail outlets in the four study districts in 2002.

	Greater Kisii	Kwale	Bondo	Makueni	Total	P values
Wall adverts*	4 (1.8%)	2 (1.0%)	2 (0.9%)	0	8 (0.9%)	0.281
Other adverts†	72 (31.6%)	73 (34.8%)	71 (32.7%)	90 (40.7%)	306 (34.9%)	0.182
With DOMC leaflets	7 (3.1%)	0	1 (0.5%)	1 (0.5%)	9 (1.0%)	0.005
With DOMC posters	10 (4.4%)	1 (0.5%)	3 (1.4%)	5 (2.3%)	19 (2.2%)	0.033
Outlet inspected last 12 months‡	67 (29.4%)	56 (26.7%)	138 (63.6%)	103 (46.6%)	364 (41.6%)	<0.001

* Does the outlet have branded wall painting advertisement for malaria products? If yes, indicate branded product(s)
† Does the outlet have branded advertising materials on display that are not wall paintings for malaria products (AM & AP brands, nets, insecticides, etc)? If yes, indicate all branded products advertised.
‡ Has the shop/pharmacy being visited in the last 12 months by MoH inspectors?

Figure 5.6: Wall advert for Malaraquin®, a brand of CQ, among other drugs.

Figure 5.7: Promotional poster for Falcidin®, (a brand of SP) and Malaratab® (an AQ brand).

5.3.8 Retailer AM dosing knowledge

Retailers were asked whether or not they would give advice on the use of drugs purchased from them. In all, 721 retailers (82.3%) said they would. These retailers were further asked to state an adult and paediatric dose for a specified product. Some shops were excluded from analysis because of non-specific responses to the questions asked; for instance "...I would give a full dose (sic) ..." without stating what the full dose was or "...swallow tablets (sic) at one go..." without stating the number of tablets, to be taken (Table 5.14). Because fieldworkers were given the discretion to choose which product to base the questions on in this section and because of differences in availability of the various AM classes (most general retailers had AQ only), equal numbers were not achieved. As such, 545 retailers were questioned on AQ, 29 retailers were queried about CQ and 147 about SP.

Retailers were more likely to refer children to health workers (50.1%) than adults (0.1%) and more likely to dose an adult correctly than a two-year old child (χ^2=463.9, df=1, p<0.001 and χ^2=38.8, df=1, p<0.001, respectively). More retailers were able to state the correct adult dose of SP (53.5%) than for AQ (32.0%) or CQ (17.9%) with significant differences between these rates (χ^2=26.8, df=2, p<0.001). This pattern was also evident for paediatric doses; more retailers could state the correct paediatric dose for SP (43.0%) than AQ (2.0%) (χ^2=86.1, df=1, p<0.001). None of the retailers could state the correct CQ dose for a two-year old child.

Table 5.14: Retailer knowledge about AM drug dosages among 721 retailers in 2002

	Correct dose	Incorrect dose	Referrals	Excluded‡	Total
Adult*					
AQ	173 (32.0%)	368	1	3	545
CQ	5 (17.9%)	23	0	1	29
SP	76 (53.5%)	66	0	5	147
Total	**254 (35.7%)**	**457**	**1 (0.1%)**	**9**	**721**
Paediatric†					
AQ	4 (2.0%)	194	278 (58.4%)	69	545
CQ	0	8	16 (66.7%)	5	29
SP	49 (43.0%)	65	27 (19.1%)	6	147
Total	**53 (16.6%)**	**267**	**321 (50.1%)**	**80**	**721**

* Do you ever give advice on how drugs in your shop should be used? If yes, what advice would you give about ___ tab/susp (*one of the AM brands stocked*) for an adult?

† For this same brand, if a mother asked you how much she should give to her child of 2 years, how would you advice her?

‡ Outlets were excluded for giving non-specific responses

For each category (adult and paediatric), data were abstracted and a univariate and multivariate analysis was undertaken to see if correct dose was independently associated with a number of parameters for which data were available from the retail audit (these are shown in Tables 5.15 to 5.17) and which could potentially influence dosing knowledge. For an adult dose, the univariate analysis revealed that retailers were almost three times as likely to give a correct response on dose for a single dose regimen like SP than they were for multiple dose regimen like AQ and CQ (unadjusted odds ratio 2.5, $p<0.001$). All variables with $p < 0.25$ in univariate analysis were further fitted into a logistic regression model (adjusted odds ratios and p values are shown in Table 5.15). Results indicate that only the type of drug (single-dose versus multiple) was significantly associated with correct dosing knowledge (adjusted odds ratio 2.38, $p<0.001$). Data for dosing for a two-year old child were treated in a similar way (Table 5.16). Although the univariate analysis showed that pharmacies (unadjusted odds ratio 3.33, $p<0.001$), presence in the outlet of DOMC posters (unadjusted odds ratio 7.18, $p<0.011$), SP (unadjusted odds ratio 38.07, $p<0.001$) and use of a reference material for dose were positively correlated with correct dose, this association was retained only for the type of drug in multivariate analysis (adjusted odds ratio 45.6, $p<0.001$). Likewise, a logistic regression analysis was carried out for the determinants of referral of children to health workers (Table 5.17). General retail outlets were 20 times more likely to refer to a health worker than were pharmacies (adjusted odds ratio 0.05, $p<0.001$) and questions on AQ and CQ were three times more likely to be referred by retailers to health workers than were those on SP (adjusted odds ratio 0.30, $p<0.001$).

Table 5.15: Univariate and multivariate analysis of various predictors of correct retailer dosing of adults.

Parameter	Univariate analysis (Unadjusted odds ratios, p values)	Multivariate analysis (Adjusted odds ratios, p values)
District	0.93, p=0.379	na[†]
Outlet location (urban/rural)	0.85, p=0.322	na
Type of outlet (pharmacy/general retail)	0.98, p=0.952	na
Presence in shop of wall adverts for malaria and malaria-related products	0.30, p=0.262	na
Presence in shop of other adverts for malaria and malaria-related products	1.06, p=0.731	na
Outlet age (in years)	0.99, p=0.324	na
Age of main seller	0.99, p=0.142[*]	0.99, p=0.527
Sex of main seller	1.22, p=0.208[*]	1.26, p=0.163
Level of education of main seller (in years)	1.05, p=0.069[*]	1.02, p=0.582
Employment duration of main seller (in years)	0.97, p=0.068[*]	0.98, p=0.340
Presence in shop of DOMC leaflets	0.51, p=0.404	na
Presence in shop of DOMC posters	0.59, p=0.370	na
Drug regimen asked about (single dose [SP] or multiple [AQ or CQ])	2.53, p<0.001[*]	2.38, p<0.01

[*]Included in a logistic regression model using Stata, Version 8.2 (Stata Corp., College Station, USA)
[†]na-not applicable

Table 5.16: Univariate and multivariate analysis of various predictors of correct retailer dosing of a two-year old child.

Parameter	Univariate analysis (Unadjusted odds ratios, p values)	Multivariate analysis (Adjusted odds ratios, p values)
District	0.93, p=0.640	na
Outlet location (urban/rural)	0.98, p=0.942	na
Type of outlet (pharmacy/general retail)	3.33, p<0.001*	0.79, p=0.585
Presence in shop of wall adverts for malaria and malaria-related products	na	na
Presence in shop of other adverts for malaria and malaria-related products	1.56, p=0.143*	0.67, p=0.308
Outlet age (in years)	1.00, p=0.894	na
Age of main seller	1.01, p=0.453	na
Sex of main seller	1.30, p=0.392	na
Level of education of main seller (in years)	1.06, p=0.262	na
Employment duration of main seller (in years)	1.02, p=0.576	na
Presence in shop of DOMC leaflets	1.69, p=0.651	na
Presence in shop of DOMC posters	7.18, p=0.011*	1.66, p=0.528
Drug regimen asked about (single dose [SP] or multiple [AQ or CQ])	38.07, p<0.001*	45.6, p<0.001
If reference material (drugs packaging, etc) was used before stating dose	2.44, p=0.003*	1.82, p=0.138

*Included in a logistic regression model using Stata, Version 8.2 (Stata Corp., College Station, USA)
†na-not applicable

Table 5.17: Univariate and multivariate analysis of various predictors of referral of a two-year old child by retailers to health workers.

Parameter	Univariate analysis (Unadjusted odds ratios, p values)	Multivariate analysis (Adjusted odds ratios, p values)
District	0.92, p=0.245*	0.96, p=0.597
Outlet location (urban/rural)	1.02, p=0.888	na
Type of outlet (pharmacy/general retail)	0.02, p<0.001*	0.05, p<0.001
Presence in shop of wall adverts for malaria and malaria-related products	1.33, p=0.708	na
Presence in shop of other adverts for malaria and malaria-related products	0.729, p=0.055*	1.13, p=0.528
Outlet age (in years)	1.02, p=0.113*	0.98, p=0.344
Age of main seller	1.02, p=0.002*	1.02, p=0.074
Sex of main seller	1.02, p=0.908	na
Level of education of main seller (in years)	1.00, p=0.990	na
Employment duration of main seller (in years)	1.04, p=0.006*	1.03, p=0.302
Presence in shop of DOMC leaflets	1.00, p=0.996	na
Presence in shop of DOMC posters	1.14, p=0.799	na
Drug regimen asked about (single dose [SP] or multiple [AQ or CQ])	0.17, p<0.001*	0.30, p<0.001
If reference material (drugs packaging, etc) was used before stating dose	1.08, p=0.642	na

*Included in a logistic regression model using Stata, Version 8.2 (Stata Corp., College Station, USA)
†na-not applicable

5.4 Discussion

In this chapter, a number of potential strengths and weaknesses in the retail sector delivery of AM services have been identified, which are presented and discussed below; with special emphasis on the implications for the new first-line AM drug, ART-LUM (Coartem®). An important caveat to the interpretation of the results in this chapter is the study limitations. About 300 outlets in the original RI database had to be replaced because they had closed (99) or they could not be traced owing to insufficient details in the database (201). This is a likely source of bias in the study. A second likely source of bias in using the RI database is the fact that new outlets established since the census would have been left out of the sampling frame for the retail audit, i.e. there is a bias against new outlets being included in the sampling frame. Indeed, Conteh & Hanson (2003) posit that such lists are notoriously unreliable in developing countries and the best way of constructing a sampling frame for studying private providers of public health products (PHPs) is a full census of all outlets in a locality backed up by regular updates to account for "new" outlets. Such an approach has for instance been used by Goodman and colleagues in Tanzania to study the retail market for antimalarial drugs (Goodman *et al.*, 2004).

Another likely source of bias, especially with regard to the stocking of drugs and their prices, is the timing of the retail audit. The study was conducted in June 2002 which is the peak malaria season in most of the study districts and when most retailers are likely to stock antimalarial drugs. The drug prices are also likely to be high in this season when there is a higher demand for antimalarial drugs than the rest of the year. Establishing seasonal variations in provision of PHPs in the retail sector calls for a longitudinal study design (Conteh & Hanson, 2003) and not the cross-sectional design used in the current study.

5.4.1 Availability of wide range of AM drugs

There was a wide range of AM oral products available nationally and in the four study districts. Over 49 brands of SP tablets were identified nationally, 30 (61%) of which were available at the district level retail outlets sampled in the four districts. Likewise, 22 brands of AQ tablets were identified during the national audit, about 13 (59%) of which were in retail circulation in the study districts. Conversely, there were brands which were in retail circulation at the district level, but which had not been identified during the central audit and which were unregistered by the PPB.

One serious consequence of a wide range of products available to largely biomedically ill-informed, rural populations is brand confusion, which may lead to unintentional repeated doses of the same drug class and consequently, dose-dependent adverse effects (Osei & Beecham, 1990). Brand confusion also leads to a delay in seeking treatment during self-medication (Mwenesi, 1993). Another inevitable consequence of multiple brands is "generic substitution". Whereas generic substitution (replacing expensive brand names for cheaper, non-branded or branded alternatives) has been fervently argued to cut prices, in a situation where the patient is uninformed, unscrupulous service providers could potentially give generic products in place of the "original" and still charge for the prices of the latter. Anecdotal evidence suggests that this indeed happens in Kenya; especially in pharmacies where staff are invariably more knowledgeable than the majority of clients they serve. For instance, while sampling drug products for a WHO sponsored multi-country study of which Kenya was part (see Chapter 6 for results of this study), investigators from the National Quality Control Laboratory were surprised that "generic" products they sampled, especially from Coast province, were priced as much as the originator brands (Dr E Ogaja, personal communication).

The most widely available AM in the retail sector was AQ sold in over 95% of outlets surveyed. AQ is a prescription-only-medication (POM) and was second-line treatment at the time of the survey. In contrast, SP, the first-line drug in 2002 was available in only 29% of outlets surveyed. The situation was found to be different in neighbouring Tanzania. A similar study carried out between May and August of 2000 when CQ was still the first-line drug for uncomplicated malaria in Tanzania, found that 33% of general retail shops and 98% of pharmacies stocked CQ, while SP, the second-line treatment, was sold in <1% of general retail shops and in 37% of pharmacies (Goodman *et al.*, 2004). This points to the fact that there is a policy-practice disconnect in Kenya in drug scheduling and in the national malaria policy. Aggressive promotion of first-line AM drugs over and above all others and restriction of access to second-line drugs may be needed to redress this situation. This was attempted by the DOMC in 2000 during the transition from CQ to SP when they actually provided named SP brands in information posters to community (see Figure 5.8 for example). There was a realisation even then that not all SP products in the market would be of good quality, therefore only those brands whose quality had been assured by NQCL were put on DOMC IEC materials. But clearly, the stocking of drugs by retailers is still driven by market forces and not by government policy decisions and preferences. Closer cooperation and consultation with local pharmaceutical manufacturers and importers of AM drugs during policy changes is required but difficult to manage because the dynamics of drug policy changes put government and industry at different ends of an 'interest spectrum'; government's interest lies in the well-being of its citizens; the pharma industry interests are in profit margins. Whereas governments change policy in a slow, ponderous and usually unpredictable way (Chapter 2), industry quite like having guarantees and predictability (which the government invariably can not give) and so have a vested interest in maintaining the *status quo* since they have drugs already in the market and need to recoup their investments, whether such drugs are failing or not. There is

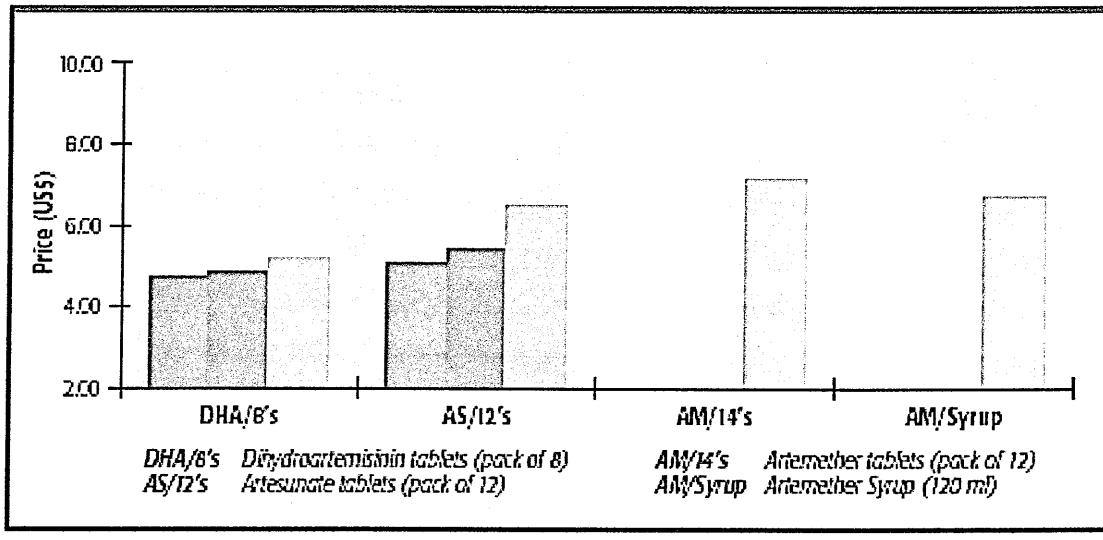
therefore a need for innovative strategies to engage industry early on in the policy change process without compromising public health.

Figure 5.8: DOMC poster with NQCL quality-assured brands of SP

5.4.2 Prices of AM drugs

The results indicate that the cheapest therapy using ART derivatives were priced at about five US dollars (368 KES) for a child of one to five years, and seven US dollars (560 KES) for an adult in the study districts. The results are consistent with a contemporaneous WHO study in Kenya for 2002 that aimed to pilot tools developed for a drug pricing methodology developed by Health Action International in collaboration with WHO. Results in Figure 5.9 indicate that the price ranges of adult patient packs of ART products were approximately five to seven US dollars, comparable to those in the present study.

Figure 5.9: Price (USD) of artemisinin antimalarial products in the private sector in Kenya (WHO, 2002)



In a study conducted in May 2000, Myhr (2000) surveyed the prices of 15 essential drugs in private pharmacies, private-for-profit hospitals, and public sector hospitals in five countries: Kenya, Uganda, Tanzania, Ethiopia, and Norway. Data from this survey on prices of AM drugs (artemether and mefloquine) in private pharmacies in Kenya were abstracted by way of comparison with the present study, i.e. the retail audit. In Myhr's study, the unit price range (one tablet) for artemether 50mg in Kenya was estimated to be between 0.62 to 0.68 US dollars which is slightly higher than in the present study (0.45-0.73), but comparable to that in neighbouring Uganda (0.47-0.72). However, the prices of originator mefloquine (Hoffmann La Roche) and generic mefloquine in Myhr's study were comparable to that obtained in the retail audit (Table 5.18). The prices from the Myhr study, however, would be higher than those in the present study if inflation over the period 2000-2002 were taken into consideration (7%, 3.3%, 1.9% in 2000, 2001 and 2002 respectively http://www.indexmundi.com/g/g.aspx?c=ke&v=71, accessed 21/06/05), suggesting that drug prices have been on the decline in real terms over this period. Generic drugs were found to be cheaper than originator products (Myhr, 2000). Figure 5.10 shows data abstracted from the retail audit for SP and AQ which reinforces the fact that generic

AM drugs are cheaper than originator AM drugs. Further, even among generics, branded generics are more expensive than those marketed under the international non-proprietary name (INN), for instance "sulfadoxine pyrimethamine tablets" or "amodiaquine tablets".

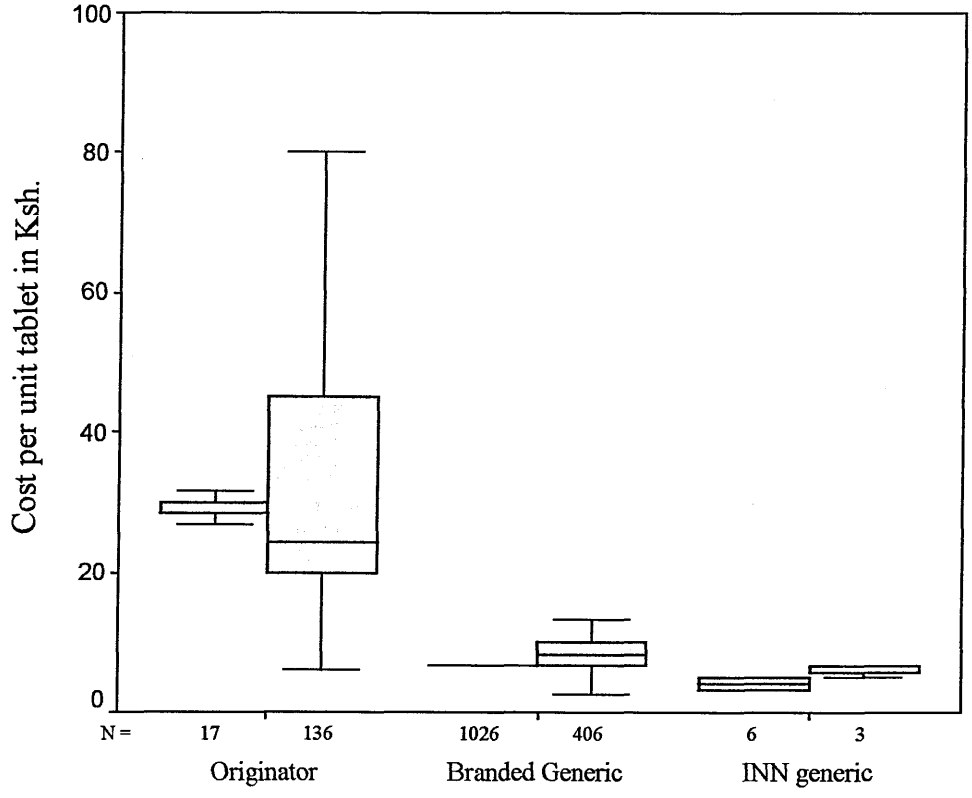
The present study showed that there were significant differences in the prices of some AM drugs at the district levels. Myhr (2000) found that the same was true at country levels and concludes that these variations were explained by the dictum "...pharmaceutical pricing is about the law of the jungle where might is right and drugs are very far from being equity priced" (Myhr, 2000). Drug prices are therefore set according to what the market can bear, whether that market is a resource-poor country's like Kenya or a wealthy nation's like Norway.

Table 5.18: Variations in unit prices (in US dollars)* and availability of tracer AM drug products in private pharmacies in five countries in 2000 compared with the Retail Audit, 2002.

	Present chapter	**Myhr 2000**				
	Retail audit 2002 (n=70)	**Kenya (n=17)**	**Uganda (n=8)**	**Tanzania (n=10)**	**Ethiopia (n=10)**	**Norway‡**
Artemether 50mg tablets USD (min, max)	0.62 (0.45-0.73)	0.64 (0.62-0.68)	0.58 (0.47-0.72)	0.88 (0.63-1.1)	na†	na
Mefloquine 250mg tablets- Roche USD (min, max)	3.7 (3.6-3.7)	3.7 (3.6-3.7)	na	5.5 (2.8-8.1)	na	3.1
Mefloquine 250mg tablets- generic USD (min, max)	1.9 (1.2-2.9)	2.0	1.8 (1.2-2.5)	3.1 (1.9-5.0)	na	na

* The Central Bank of Kenya mean exchange rate of the KES to USD was 78.8 at the time of survey.
† na-not available
‡ Norwegian retail prices were abstracted from the official price list

Figure 5.10: Differences in the 2002 unit prices (in KES) of generic and originator products for SP (500/25mg tablets, green) and AQ (200mg tablets, red) in Kenya. CBK mean exchange rate to the US dollar was 78.8 KES on June 28, 2002.



INN-international non-proprietary name i.e. amodiaquine, mefloquine, etc.

In contrast to the price of ARTs, the first-line therapy of SP in June 2002 was less than one US dollar per adult treatment course (20 to 40 KES). This has created expectations that therapies for malaria must be considerably less than a dollar. This of course raises issues in terms of affordability to the public of new ART combinations all of which are in excess of one USD per adult treatment course. The retail sector is an important source of treatment and it seems unlikely that poor households would be able to afford the new therapy over the counter. Even in the government sector, this has policy implications and financial sustainability has resulted in a delay in policy implementation of the new ART-LUM policy in Kenya (Section 2.7.3.2). Greater access to these products by way of bulk purchase through the government sector (as is currently the arrangement with WHO and

Novartis) or regulatory measures that down-regulate ART products to OTC status (as is planned after studying the safety of ART-LUM under operational use in Kenya) might benefit from economics of scale thus bringing the prices down.

Four-dose ART-LUM (see private sector Coartem®, Figure 3.5) was found in eight district level pharmacies (i.e. 11% of pharmacies) in Greater Kisii, Bondo and Kwale (but not in Makueni) at a median price of 600 KES (7.6 USD, interquartile range 492 KES (6.2 USD), 794 KES (10.1 USD). Overall, there were no variations in the prices of ART derivatives and combinations like ART-LUM between the districts. This is probably because ARTs were available only in pharmacies where retail mark-ups are more uniform than in general retail shops. The Pharmaceutical Society of Kenya (PSK) recommends that retailers put a 33% mark-up on the trade price of medicines and an additional dispensing fee of KES 20 per prescription for POM drugs (Kimotho *et al.*, 2002), although Myhr reports mark-ups of 15% among wholesalers in Kenya and 20% among retailers (Myhr, 2000). The profit margin of ARTs on the cheapest national prices was 29% in this study, comparable to the PSK recommended mark-up. Down regulation of Coartem® from POM to OTC to increase access in general retail shops is likely to result in wide variations in prices since "pharmaceutical pricing is about the law of the jungle" (Myhr, 2000). The results also demonstrate that drug scheduling in Kenya is largely ineffective. AQ a POM drug and second-line at the time of the study was available in over 95% of shops, yet SP, the first-line drug, which was OTC, was relatively unavailable. This lack of adherence to drug schedules will further encourage leakage of public sector Coartem® into the private sector where there will be a ready market and where the application of rules is lax.

A surprise finding that opens opportunities for increased regulation of the retail sector to detect 'leakage' was the fact that a high proportion of retailers across all the districts

reported that they were visited by MoH personnel in the preceding 12 months (30 to 64%). Although the precise nature of these visits is still unclear, anecdotal evidence from the retailers suggests that inspectors usually instruct retailers to remove expired drugs or failed drugs like CQ from the shelves. Good inspection rates can be used to reinforce key drug policy messages to ensure a better chance of programmatic success.

Differences were noted between pharmacies and general retail shops in terms of drug sources and drug ranges, with pharmacies getting their drug supplies from wholesale pharmacies and general retail shops obtaining theirs from general wholesalers. This has also been noted in neighbouring Tanzania (Goodman *et al.*, 2004). Pharmacies also had a wider range of antimalarial products. However, there were no discernable differences between pharmacies and general retail shops in terms of product prices and retailer knowledge of antimalarial drugs. Given the *de jure* licensing and inspection requirements for pharmacies in Kenya, one would expect that they be manned by well qualified staff with better knowledge of antimalarial drugs than is the case for general retailers. It seems from the results however that such regulations are only "on paper" and not properly enforced, an observation made in Chapter 3 with regard to drug registration and post-marketing surveillance and in this Chapter with regard to enforcement of prescription-only status of AQ. There is need to engage the Pharmacy and Poisons Board and other regulatory bodies to ensure the success of the national antimalarial drug policy.

5.4.3 Retailer knowledge of AM dosage

Of concern for OTC drugs generally is the poor knowledge of AM drug use by shopkeepers especially with regard to paediatric use (Marsh *et al.*, 1999). Whereas approximately a third of the general retailers interviewed in the present study could state the correct AQ dose for adults, less than 2% could state the correct dose for a two-year old

child. The logistic regression models also revealed that the type of drug (single dose versus multiple doses) was the biggest predictor of correct dosing and of referral to health workers; they were more likely to get SP dose correct than the multiple dose regimen. One limitation of the present study, however, was that direct questioning about normal practice was used rather than simulated client surveys, which would probably have been a better method of investigating retailer behaviour. It has been observed that asking service providers hypothetical questions has an element of bias since respondents tend to give "socially desirable" responses, i.e. they overestimate what they think is expected of them and underestimate what they think they ought not to do or say, as such the rates given here are probably overestimates. Such response bias is minimised in simulated client surveys where real-life scenarios are presented to service providers by way, for example of a 'sick' adult (decoy), and drugs being actually purchased or dispensed. In such surveys, actual practice is therefore captured (Madden *et al.*, 1997).

There are only a few studies on retailer knowledge of AM drugs in Kenya and the few that have been done are not exactly comparable. Marsh *et al.* (1999) for instance used the proportion of retail clients who purchased an adequate dose of AM in Kilifi (as opposed to a hypothetical patient in the retail audit) or proportion of clients who reportedly adhered to retail-bought AM drugs from community-wide cross-sectional surveys (Section 2.5.2). Nonetheless some broad similarities and differences can be drawn. The present retail audit in four study districts was comparable to the pre-training period of the Kilifi study in Table 5.19, which shows that although retailer knowledge of AM is concordant with those who purchased correct dose in Marsh's study (29.8% versus 31.8%), the proportion of retailers who gave advice were different between the present retail audit and the Kilifi study. However, the sample size for advice on AM was very small in the Kilifi study compared to the retail audit. Included in Table 5.19 are the results of retailer knowledge after a

programme of retailer training on dosing knowledge and general advice. Post-training follow-up in Kilifi revealed that these gains were maintained over time with 86 to 99% of trained retailers giving correct dose of AM drugs (Marsh *et al.*, 2004). Similar studies in Bungoma have shown that although retailer knowledge of AM dosing is poor, this can be improved with minimal training and resource input (Tavrow *et al.*, 2003).

Marsh's study in Kilifi is part of a wider KEMRI/Wellcome Trust and DOMC collaboration that aims to improve antimalarial service delivery in the retail sector. The initial pilot studies in Kilifi were funded by the DfID. In July 2004, this study was scaled-up to five other districts: Kwale, Busia, Makueni, Gucha and Nandi North, using funds availed through the Round II application to the Global Fund for AIDS, TB and Malaria (GFATM). Further, between July and November 2004, the DOMC conducted a training of trainers (TOT) workshop for district public health officers and district health education officers from Nyanza, Western and Rift Valley provinces and it is hoped that the programme will be scaled-up to the national level using this strategy (Mr B Adika, personal communication).

Table 5.19: Retailer knowledge about AM drug use in Kilifi and in the Retail audit study districts.

	Marsh *et al* (1999) Kilifi			**Retail Audit 2002 Greater Kisii, Kwale, Bondo, Makueni**
	Before Training Dec/Jan 95/96	**After training June/July 1999**	**After training Dec/Jan 96/97**	**No training‡**
Give advice on use of AM drug	2.0% (0.4-3.6)†	93.5% (88.8-96.3)	97.5 (92.3-99.3)	82.3% (79.6-84.7)
Purchase adequate dose* of AM (all AM sales)	31.8% (26.6-37.6)	82.7% (76.3-87.3)	89.9% (82.7-94.4)	29.8% (27.0-32.7)

*Adequate dose according to national standard treatment guidelines
† Fleiss-Quadratic 95% confidence intervals
‡ Retailers in the audit were assumed not to have been trained for lack of information

ART-LUM, the new first-line AM policy, is a multiple dose regimen and retailers are therefore likely to give poor advice to retail clients on its use, based on the results of this chapter. If ART-LUM is deregulated and made available as an OTC drug (Section 3.4.4), then clear, unambiguous training materials and retailer training programmes would be required to make retail outlets function as appropriate outlets for ACTs. The univariate analysis did show that the presence in the retail outlet of DOMC posters was associated with correct dosing for a two-year old child. Although less than 5% of outlets had these posters, this positive correlation points to the fact that well-designed IEC materials do make a difference in malaria control.

5.5 Summary

Although an important source of treatment for fevers and malaria, the Kenyan retail sector is fraught with a number of weaknesses that are likely to mitigate against appropriate case-management of malaria in the home. Drugs availed through the retail sector follow client demand, which is not always in line with policy. It is evident that AQ was in higher demand in the retail sector than SP, the first-line dug at the time. This coupled with poor retailer dosing knowledge of multiple dose regimens is likely to impact negatively on the implementation of the newly launched policy involving a 6-dose drug regimen. The fact that drug schedules are not adequately enforced (since POM drugs are available OTC) also means that public sector ART-LUM might leak into the private retail sector where drugs are not equitably priced, but where pricing follows the laws of the jungle and where "might is right". A similar situation prevails for ITN. The KEMRI/Wellcome Group in collaboration with other stakeholders and with the DOMC has pioneered a shop-keeper retailer programme in Kilifi to try and redress some of these deficiencies. This has being scaled-up to five other districts and it is envisaged to cover the rest of the country in the near future, but clearly, training alone is not enough. Strategies are needed to better engage

the local pharmaceutical manufacturers and drug importers in drug policy changes, although this, as discussed earlier, is fraught with its own challenges. There is a need for more equitable pricing of drugs and non-drug commodities and the role of price controls in redressing this needs to be investigated further. In addition, there is a need for stricter and wider inspections of drug distribution channels to reign-in the unscrupulous trade in errant drugs, to stop leakage of public sector drugs into the private sector, and to ensure drugs are stocked according to national policy. All these strategies need to involve the community by way of clear and unambiguous IEC materials from the DOMC.

CHAPTER 6:

Quality of antimalarial drugs in the Kenyan retail sector

6.1 Introduction

The quality of essential drugs available over-the-counter to populations at risk is receiving a renewed international interest (WHO, 1999b; 1999c) and is the cause of major political and public health concern in several countries including Kenya (http://www.nationmedia.com, accessed 19/11/04; http://www.allafrica.com, accessed 19/11/04). Several reports have cast doubt on the quality of drugs in the Kenyan market in general (Kibwage *et al.*, 1988; 1991; 1998) and that of antimalarial (AM) drugs in particular (Kibwage & Ngugi, 2000).

The debate on the quality of essential drugs especially intensified in June 2001, just before and following the passing of the Kenya Industrial Properties Bill 2001, which sought to improve access to these products (and especially generic antiretroviral drugs, ARVs) through parallel importation by, and compulsory licensing of local pharmaceutical firms. Since a significant fraction of the generic drugs sold in Kenya are imported from other developing countries, concerns had been raised on the quality of such generic drugs, which include ARVs. This concern has been compounded by the limited capacity of the existing government departments to ensure that only drugs of proven quality are available to the public through a strict registration process, as indicated by the presence in the market of unregistered products (Chapter 5). The quality of AM drugs in Kenya is therefore part of a wider drug quality and regulation problem (Chapter 3).

The Ministry of Health (MoH) has highlighted in the Kenya National Malaria Strategy (KNMS) that it will be committed to guaranteeing access to quality controlled AM products through a joint effort by the DOMC, the Pharmacy & Poisons Board (PPB), and the National Quality Control Laboratory (NQCL) (Section 2.4.3). To-date, the few studies that have been done on the quality of AM drugs in Kenya, and in the sub-region, have been

ad hoc, focused on products found in major urban centres or those submitted to the PPB for purposes of registration (reviewed in Section 1.9). There has been a dearth of independent studies on the quality of OTC AM drugs available at the peripheral (district) retail level where malaria therapies are routinely sought. This chapter describes the quality of AM products containing sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) available in the retail sector. SP and AQ were the first and second-line treatment for uncomplicated malaria in July 2002 when the study was conducted.

6.2 Materials and methods

The sampling of products was done between February and May 2002 coincidental with the first round of the retail audit survey (Chapter 5); the four study districts are described in detail in Chapter 4.

6.2.1 Sampling drug products

Products containing SP and AQ were purchased from wholesale outlets identified during the pre-sensitisation rounds of the retail audit (Section 5.2.2.2). Data obtained from this first round were assessed in terms of a frequency distribution of common products and major wholesale suppliers for AQ and SP products separately for each district. The top 10 wholesalers for AM products in each district were visited to purchase AQ and SP branded products and a simple proforma completed on details pertaining to the wholesale supplier (Appendix IV). To cover as many products as possible, if a given product had been purchased from the preceding district or wholesaler, preference was given to the one, which had not been hitherto sampled. Between 60-100 tablets, or 7-10 bottles of suspensions/syrups/drops, of each product of interest were purchased. The price of the product (s), the date of purchase, quantity, and storage conditions were recorded on the proforma. The samples were each provided with a unique identifier

(district+wholesaler+product) and details of packaging, manufacturer, manufacture date, expiry date, whether they contained dosing schedules and so on, were entered into a database (Microsoft-Excel 2000, Microsoft Corp., Redmond, USA). Drug samples were first subjected to visual inspection to assess factors predictive of poor quality drugs and then evaluated by standard United States Pharmacopoeial tests (USP, 2000) described below.

6.2.2 Visual inspection

This entailed taking details of packaging, quality of labelling and pharmaceutical elegance of the samples (broken tablets, discolouration, mottling, sedimentation, etc). These were entered into a standard database and compared with the outcome of the standard pharmacopoeial tests described below.

6.2.3 Laboratory methods

6.2.3.1 Reagents

Reference standards of sulfadoxine (Lots F-1 and F-2), pyrimethamine (Lots G and H) and AQ hydrochloride (Lot G-1) were purchased from the United States Pharmacopoeial Commission, Rockville, MD, USA. Phenacetin (Lot 13615-018) was purchased from the Sigma-Aldrich Chemicals Co. Dorset, United Kingdom. All other reagents and solvents were either of analytical or high-pressure liquid chromatographic (HPLC) grades and were purchased from BDH Chemicals Limited, Poole, UK.

6.2.3.2 Analytical methods

USP test for content

Content tests essentially determine the amount of active ingredient in a product, which is expressed as a percentage of the label claim. Sample preparation and assay for SP and AQ

were performed according to USP specifications (USP, 2000). SP was assayed by HPLC while AQ was assayed spectrophotometrically (UV/VIS PU8725 Philips scientific, Cambridge, UK). The HPLC system consisted of a HP 1050 Pump (Hewlett Packard GmbH, Waldbronn, Germany) equipped with a Rheodyne injector (model 7125) with a 20 µL loop (Rheodyne), HP 1050 variable wavelength UV/VIS detector set at 254nm (Hewlett Packard GmbH, Waldbronn, Germany). A Hypersil BDS RP_{18} 5 µm (250 x 4.6 mm ID) (Thermo Hypersil –Keystone, UK) column attached to a Lichrosopher 100 RP_{18} 5 µm guard column (Merck, Germany) immersed in a water-bath or enclosed in a column heater at 40 °C was used as a stationary phase. The mobile phase consisted of a mixture of acetonitrile and 5% glacial acetic acid (25:75v/v) delivered at a flow rate of 2.0 ml/min. The mobile phase was degassed by ultra-sonication before use. A computer equipped with HP Chemstation program for LC systems was used to process and store data on the generated chromatograms.

USP Dissolution test

Dissolution tests are done to determine the amount of active ingredient that is available for absorption and are used as surrogate markers of *in vivo* bioavailability. Tests were done for tablet formulations only. A six-station Erweka DT 600 dissolution apparatus (Erweka Gmbh, Frankfurt, Germany) was used. For SP, the dissolution medium was 1000ml phosphate buffer, pH 6.8 (USP, 2000) maintained at 37 ± 0.5 °C, while for AQ 900ml of distilled water maintained at 37 ± 0.5 °C was used as the dissolution medium. Paddle speed was set at 75 revolutions per minute (rpm) for SP and 50 rpm for AQ and amount of active ingredient in solution determined after 30 minutes.

6.3 Data analysis

Drug product content (% label claim) and tablet dissolution rates were estimated as described in the USP (USP, 2000). USP specifications give dichotomous outcomes: either a product has passed or failed the requisite tests. Further analysis was performed to investigate whether there was any association between several product aesthetic factors (like packaging) and the outcome of the USP tests (passing/failing according to USP specifications). The analysis also included comparisons, based on the above specifications, between locally manufactured products and those imported into the country using simple chi-squared tests and logistic regressions. Stocking frequencies for AM products (used in sampling products) were expressed in terms of the number of outlets selling a particular product at the time of the retail audit survey (2002).

6.4 Results

6.4.1. Sampling products for chemical analysis

Table 6.1 shows the most common (top five) AQ and SP products encountered in the retail sector during the first round of the survey on which sampling drug products for QC was based. Results demonstrate that 1) the generic product Malaratab® was the most frequently encountered AQ product while Falcidin® was the most frequent SP product and that 2) tablet formulations predominated compared to the suspensions. Both Malaratab® and Falcidin® are manufactured locally by Cosmos Pharmaceuticals Limited.

For SP tablets, 23 brands were encountered of which 19 (82.6%) were sampled for analysis. For AQ tablets, 13 brands were encountered of which 11 (84.6%) were sampled for analysis. Likewise, for the liquid formulations, 13 SP suspensions/paediatric drops were encountered of which 12 (92.3%) were sampled; 12 AQ suspensions were encountered of which 11 (91.7%) were sampled for analysis. The sampling method used

therefore yielded good brand or product coverage. Unbranded generic products (those using the International Non-proprietary Name, INN) were not sampled for analysis.

Table 6.1: Stocking frequencies of top five common SP and AQ branded products across 856 retail outlets visited during the initial round of the retail audit survey in 2002. Data presented as proportion of audited retail outlets stocking a given product.

SP		AQ	
Brand	**Stocking frequency***	**Brand**	**Stocking frequency***
Tablets		**Tablets**	
Falcidin®	159 (18.6%)	Malaratab®	735 (85.9%)
Fansidar®	81 (9.5%)	Betaquine®	115 (13.4%)
Metakelfin®	54 (6.3%)	Alphaquine®	37 (4.3%)
Orodar®	49 (5.7%)	Emoquin®	23 (2.7%)
Malodar®	16 (1.9%)	Camoquin®	17 (2.0%)
Others	115 (13.4%)	Others	42 (4.9%)
Suspensions		**Suspensions**	
Pyralfin®	20 (2.3%)	Amobin®	30 (3.5%)
Falcigo®	14 (1.6%)	Malaramed®	24 (2.8%)
Falcidin®	13 (1.5%)	Malaratab®	17 (2.0%)
Intadoxin®	12 (1.4%)	Falciquin®	16 (1.9%)
Medifan®	11 (1.3%)	Kamoc®	13 (1.5%)
Others	41 (4.8%)	Others	34 (4.0%)

* Proportion of audited outlets stocking a given product

Tables 6.2 and 6.3 give further details of the samples collected, their manufacturers, countries of origin, formulations, and number of batches sampled. About half the SP brands (48%) were imported from the Indian sub-continent, with most of the remaining being manufactured in Kenya (48%) and one brand (Fansidar®) was imported from Switzerland (Table 6.2). In contrast, 80% of AQ brands sampled were locally manufactured (Table 6.3).

Table 6.2: Manufacturers, countries of origin, formulations, strengths and batches of 64 SP samples analysed following the retail audit in 2002.

Brand (Manufacturer, Country of Origin)	Formulation	Strength	Number of unique batches tested
Amalar® (Brown & Burke, India)	Tablets	500mg/25mg	2
Falcidin® (Cosmos, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	4 4
Falcigo® (Biodeal, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	1 3
Fanlar® (Dawa, Kenya)	Tablets	500mg/25mg	2
Fansidar® (Roche, Switzerland)	Tablets	500mg/25mg	4
Falcimax® (Sphinx, Kenya)	Suspensions	250mg/12.5mg per 5ml	3
Fansimax® (Maxs, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	1 1
Intadoxin® (Regal, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	1 3
Lansidar® (Ekta Exports, India)	Suspensions	250mg/12.5mg per 5ml	1
Lansidar® (Unibios, India)	Suspensions	250mg/12.5mg per 5ml	1
Laridox® (Ipca, India)	Tablets	500mg/25mg	1
Malareich® (Smithkline Beecham, India)	Tablets	500mg/25mg	3
Malastin® (Emil, India)	Tablets	500mg/25mg	1
Malidar® (Umedica, India)	Tablets	500mg/25mg	2
Malidar® (Gracure, India)	Suspensions	250mg/12.5mg per 5ml	2
Malodar® (Lab & Allied, Kenya)	Tablets	500mg/25mg	3
Malostat® (Intas, India)	Tablets	500mg/25mg	1
Medifan® (Medivet, Kenya)	Suspensions	250mg/12.5mg per 5ml	2
Methomine-S® (Universal Pharmacy, Kenya)	Tablets	500mg/25mg	1
Nopyrin® (Flamingo, India)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	1 1
Orodar® (Elys, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	2 2
Pyralfin® (Lupin, India)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	1 2
Unidar® (PMC, Kenya)	Tablets Suspensions	500mg/25mg 250mg/12.5mg per 5ml	3 2
Viparum® (Universal Pharmacy, Kenya)	Tablets	500mg/25mg	2
Viparum® (Unknown*, India)	Tablets	500mg/25mg	1

*Only local agent identified by name (Bulk Medicals, Kenya), not manufacturer.

Table 6.3: Manufacturers, countries of origin, formulations, strengths and batches of 52 AQ samples analysed following the retail audit in 2002.

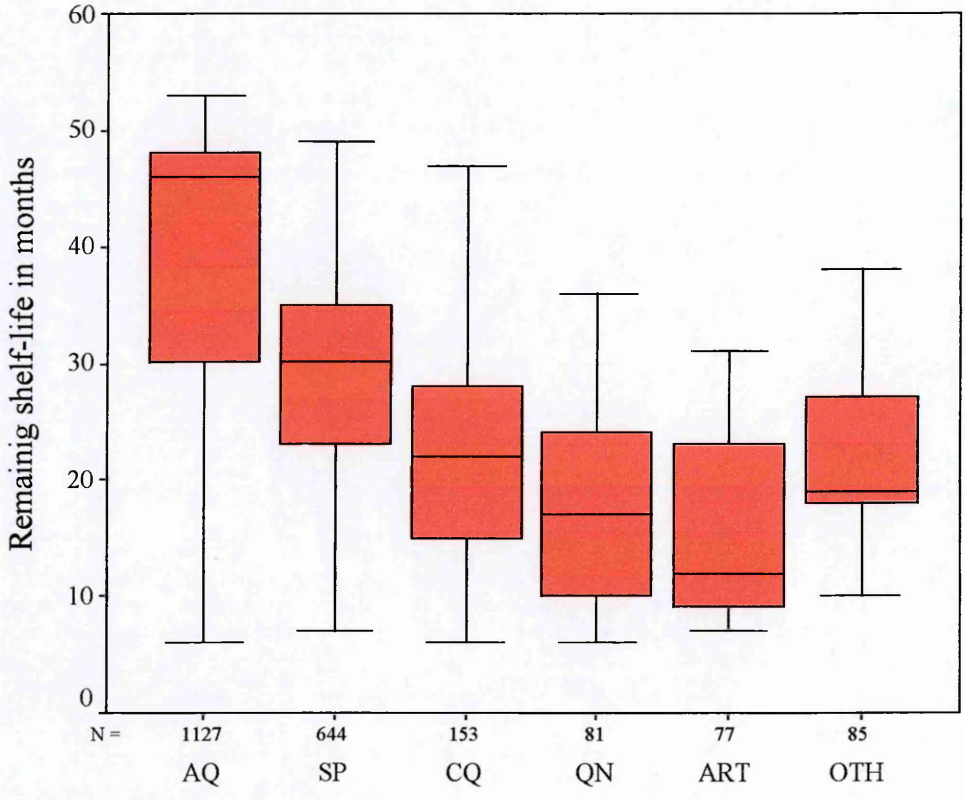
Brand (Manufacturer, Country of Origin)	Formulation	Strength	Number of unique batches tested
Alphaquine® (Dawa, Kenya)	Tablets	200mg	1
Amobin® (Regal, Kenya)	Tablets Suspensions	200mg 50mg per 5ml	3 4
Amoquin® (Novelty, Kenya)	Suspensions	50mg per 5ml	1
Amowin® (Caplin Point, India)	Tablets	200mg	1
Betaquine® (Beta Healthcare, Kenya)	Tablets	200mg	4
Camoquin® (Parke-Davis, Senegal)	Tablets Suspensions	200mg 50mg per 5ml	4 3
Diaquin® (Maxs, Kenya)	Tablets	200mg	1
Emoquin® (Elys, Kenya)	Tablets Suspensions	200mg 50mg per 5ml	3 2
Falciquin® (Sphinx, Kenya)	Suspensions	50mg per 5ml	3
Kamoc® (Gracure, India)	Tablets Suspensions	200mg 50mg per 5ml	2 1
Laeoquin® (Lab & Allied, Kenya)	Tablets Suspensions	200mg 50mg per 5ml	2 1
Malarabit® (Biodeal, Kenya)	Suspensions	50mg per 5ml	1
Malaramed® (Medivet, Kenya)	Suspensions	50mg per 5ml	4
Malaratab® (Cosmos, Kenya)	Tablets Suspensions	200mg 50mg per 5ml	6 2
Uniquin® (PMC, Kenya)	Tablets Suspensions	200mg 50mg per 5ml	2 1

6.4.2. General quality of AM products: shelf life and storage conditions

In the main retail audit survey (Section 5.2.3), information was collected on product storage conditions and shelf life. Of 2,401 audited oral AM products, 234 (9.7%) had expired by the time of the survey (June 2002). Figure 6.1 shows median remaining shelf-life (in months) of the remaining 2,167 AM products by chemical group. Overall, AQ products had the longest remaining shelf life (46 months, interquartile range [IQR] 30, 48), followed by SP (median 30 months, IQR 23, 35). Chloroquine (CQ), quinine (QN), and

"other" products (OTH in the figure refers to mefloquine, halofantrine, proguanil and mepacrine) had remaining shelf lives of 22 (IQR 15, 28), 17 (IQR 10, 25) and 19 (IQR 18, 27) months, respectively. Products containing artemisinin (ART) had remaining median shelf life of 12 months (IQR 9, 23). The majority of products (97.2%) were found to satisfy the basic storage conditions set out in the study (namely stored off the floor, out of direct sunlight, in a dry area and away from food stuffs).

Figure 6.1: Shelf life of 2,167 audited, un-expired oral AM products in 876 retail outlets in four districts of Kenya by chemical group.



6.4.3 Chemical analyses

The results for the analysis of SP and AQ for active ingredient content and tablet dissolution rates are summarised in Tables 6.4 and 6.5, respectively. Overall, 116 samples of SP and AQ were analysed in 2002 for content and dissolution of which 47 (40.5%) did

not meet the USP specifications for content and/or dissolution. Details are given in the following sections for each drug class separately.

6.4.3.1 SP samples

Sixty-four SP samples were analysed by HPLC (37 tablet batches and 27 suspensions). For dissolution, six different solutions were each analysed once and for the content determination, two different solutions were each analysed three times. The amount of active ingredient released in 30 min was calculated by comparison with the USP chemical reference substance with an assigned purity of 100%. The USP monograph acceptance criteria (6 tablets) for SP require that the amount released in 30 minutes for sulfadoxine (SDX) or pyrimethamine (PMT) should be at least 60 % of label claim and that the content of SDX or PMT in any sample should be 90 – 110 % of label claim. Overall, 45.3% of SP samples failed to meet these criteria. For the tablet forms 13 (35.1%) samples failed to meet the official requirements: 10 samples (76.9% of failures) failed dissolution alone, 2 (15.4%) samples failed content alone, and 1 (7.7%) failed both tests. A disproportionate percentage of SP products failing dissolution and content tests (90% and 100%, respectively) had problems with the PMT component. Further, the only sample, which failed both dissolution and content, did so with respect to PMT alone.

Twenty-seven (27) SP suspensions were analysed for content (limits 90-110% of L.C). Results in Table 6.5 show that sixteen samples (59.3%) failed to meet official requirements: 0 (0% of failures) with respect to the SDX component only, 13 (81.3%) with respect to PMT only and 3 (18.7%) with respect to both active ingredients. One sample had no detectable PMT and can only be said to be substandard (not counterfeit) according to the WHO, which defines fake or counterfeit drugs as those "...deliberately and fraudulently

mislabelled with respect to identity and/or source..." (WHO, 1999c). The bulk of SP failures can again be attributed to PMT (Table 6.4).

Table 6.4: Results of 37 SP tablets and 27 SP suspensions analysed in 2002. Amount sulfadoxine (SDX) and pyrimethamine (PMT) is expressed as percent label claim. USP limits for content of SDX and PMT range from 90-110% and amount SDX/PMT released into dissolution medium within 30 min should be >= 60%. Pass means within limit, and low and high fail means lower or higher than limit , respectively. na=not applicable.

	Content						Dissolution			
	Low fail		Pass		High fail		Low fail		Pass	
	SDX	PMT	SDX	PMT	SDX	PMT	SDX	PMT	SDX	PMT
SP tablets	0	3 (8.1%)	37 (100.0%)	34 (91.9%)	0	0	1 (2.7%)	11 (29.7%)	36 (97.3%)	26 (70.3%)
SP suspensions	2 (7.4%)	12 (44.4%)	21 (77.8%)	12 (44.4%)	4 (14.8%)	3 (11.1%)	na	na	na	na

6.4.3.2 AQ samples

Fifty-two (52) AQ samples (29 tablet forms and 23 suspensions) were analysed spectrophotometrically. The results obtained for the samples are presented in Table 6.5. For dissolution, six different solutions were each analysed once and for the content determination, two different solutions were each analysed three times. The amount (% L.C.) released in 30 minutes and content (% L.C.) of AQ were calculated by comparison with the USP chemical reference substance with an assigned purity of 100%. The USP monograph acceptance criteria (6 tablets) for AQ require that the amount released in 30 min for AQ should be more than 75% of the LC and the content of AQ in all samples should be 93–107% of LC. Results show that 11 (37.9%) tablet samples failed the requisite tests: 1 (9.1% of AQ tablet failures) for dissolution alone, 7 (63.6%) for AQ content alone and 3 (27.3%) failed both tests. Results indicate that 7 (30.4%) suspensions failed the content test with 6 (85.7% of failures) being below the lower limit and one sample above the higher limit (Table 6.5).

Table 6.5: Results of 29 AQ tablets and 23 AQ suspensions analysed in 2002. Amount AQ is expressed as percent label claim. USP limits for content of AQ range from 93-107% and amount AQ released into dissolution medium within 30 min should be >= 75%. Pass means within limit, and low and high fail means lower or higher than limit , respectively. na=not applicable.

	Content			Dissolution	
	Low fail	**Pass**	**High fail**	**Low fail**	**Pass**
AQ tablets	10 (34.5%)	19 (65.5%)	0	4 (13.8%)	25 (86.2%)
AQ suspensions	6 (26.1%)	16 (69.6%)	1 (4.3%)	na	na

6.4.4 Visual inspection: factors associated with poor quality drugs

Due to the limited number of samples and the attendant limited Events Per Variable (EPV), only 4 factors were included in a logistic regression model with the outcome variable being whether a sample passed or failed the USP requirements. As a rule of thumb, at least 10 EPVs are required for good model prediction (Peduzzi *et al.*, 1996). The results were inconclusive; none of the explanatory variables (retail prices, import status of the product, signs of physical instability, presence of expiry dates on package) were statistically associated with a poor outcome (Table 6.6).

Table 6.6: Characteristics of samples passing or failing the USP specifications for dissolution and/or content.

Variable	**Number of observations**	**Failure rate**	**P value (univariate)***	**P value (multivariate)**
Mean retail price per unit†	Passed-69 Failed-47	12.5 (7.5) 12.5 (9.2)	0.789	0.916
Local vs. Imported products	Local-80 Imported-36	Local-42.5% Imported-36.1%	0.197	0.477
Expiry indicated	No expiry on pack-8 Expiry on pack-108	No expiry on pack-25.0% Expiry on pack-41.7%	0.580	0.493
Physical instability‡	Absent-83 Present-33	Absent-37.3% Present-48.5%	0.372	0.389

*Pearson's Chi-square for proportions and one-way ANOVA for mean.
†Unit consisted of a tablet or 5ml of suspension.
‡For tablets signs of physical instability included swelling, fusion, mottling, etc. For suspensions, lack of uniformity of colour, sedimentation, etc.

6.5 Discussion

Drugs are an essential health commodity and the vagaries in their performance attract a lot of public attention. Figure 6.2 shows examples of newspaper headlines that appeared in December 2001 in the Kenyan press about drugs expiring in the Kenya Medical Supplies Agency's central warehouses in Nairobi. Such headlines are not restricted to Kenya alone. The same concerns about quality of drugs was raised in the USA in 2003 following imports of fake drugs by health management organisations from outside the USA (mostly Mexico.) (http://www.bbc.co.uk, accessed 07/12/04)

Figure 6.2: Public concern about drug quality, an example of newspaper headlines in Kenya

6.5.1 General quality and shelf life

The results suggest that product expiration is a problem in the retail sector; about 10% of products audited in the main retail survey were past their expiry dates. However, the majority of products stocked (97%) were found to satisfy the basic storage conditions set out in the study (namely stored off the floor, out of direct sunlight, in a dry area and away from food stuffs).

It is important to note that the manufacturer's "shelf life" applies only to products whose integrity has not been breached, i.e. products should be in their original containers (e.g. blister pack). Once this integrity is breached, shelf life no longer applies. This is especially important for the artemisinin derivatives, which take up, and react with water thus making them less effective. It is even more important for AQ, which on reaction with water forms a toxic quinone imine metabolite implicated in adverse reactions to AQ (Maggs *et al.*, 1987; Christie *et al.*, 1989; Winstanley *et al.*, 1990).

6.5.2 Chemical analyses

One main limitation of the chemical analyses is the fact that a test for impurities was not done. Impurities can arise as by-products of the manufacturing process or may be because of a chemical reaction (with light, air, water) whilst the product is in storage. A key impurity in Aspirin (acetyl salicylic acid) for instance, and whose content has to be limited in the final product is salicylic acid, a potentially toxic compound. Whilst in storage, aspirin can also be hydrolysed by moisture to form this parent compound; adrenalin undergoes auto-oxidation if exposed to light, thus its storage in amber-coloured bottles; a cyanide salt is used as a raw material in the manufacture of chlorproguanil. Limiting impurities therefore is an important aspect of quality assurance.

The above limitation notwithstanding, the content and dissolution tests reveal a large number of substandard AQ and SP products in the market (40.5%) which is consistent with reports of substandard essential drugs across the developing world (Taylor *et al.*, 2001). These results also suggest that for SP products, pyrimethamine accounts for a disproportionate number of dissolution and content failures. A similar problem has also been noted by other workers, and it has been suggested that this is due to the poor solubility of pyrimethamine (Kibwage & Ngugi, 2000; WHO, 2003d).

Of particular concern is the poor quality of SP suspensions in the market; 59.3% failed to meet the official requirements, especially with regard to the pyrimethamine component. This is despite the fact that during analysis, an ideal situation is simulated. The suspensions are first ultra-sonicated to evenly disperse the active ingredient and then the content of active ingredient in a given volume of suspension (equivalent to a given weight of active ingredient) is determined. In practice, mothers will not be able to replicate such ideal conditions. Moreover, there were sedimentation problems with most suspensions sampled in the survey. In addition, it is known that there is great variability in the 'tea spoons' that mothers use to measure suspensions for their children (Kabati *et al.*, 1998). There is therefore need for greater controls on the quality of AM suspensions in the market since the burden of malaria is greatest in children under five who are expected to use these preparations.

Also in line with previous reports is the finding that no differences existed between the quality of local and imported products (WHO, 2003d), suggesting that the phenomenon of poor quality drugs is one that is common to many countries or that products intended for export to developing countries are not manufactured to the same standards as those consumed in the exporting countries (WHO, 1995). Although a substantial proportion of

samples did not comply with the USP specifications, most products, which failed, did so marginally. In general, more products failed by being below the required specifications compared to those, which failed by being above the required specifications. These failures can be attributed to poor quality control during manufacture (Kibwage & Ngugi, 2000; Taylor *et al.*, 2001), and reflects the fact that most developing countries including Kenya have limited regulatory mechanisms for enforcing Good Manufacturing Practices (GMP).

In Kenya, there are about 40 pharmaceutical manufacturing plants. The pharmaceutical Inspectorate department of the Pharmacy and Poisons Board is still in its infancy and even a dedicated team can inspect a given plant at most once a year. The presence in the market of poor quality drugs also gives credence to an oft-repeated comment in Kenya that manufacturers and suppliers tend to put forward very good samples at registration, and then do not adhere to GMP once the drug is registered. There is a need for local industries to invest in GMP requirements and subsequently encourage them to adhere to GMP standards, and for the MoH to support its drug regulatory arm by providing additional financial and human resources to not only enforce GMP, but to carry out stringent checks on products in circulation. Since most drugs are imported from abroad, there is need to tighten controls at ports of entry. One possible and cheap way of detecting poor quality drugs at ports of entry is through the use of semi-quantitative tests such as the Mini-Lab™ which relies on simple colour reactions to quickly identify substandard products (Jahnke & Kusters, 2001). However, as has been stated earlier, such tests will not be able to distinguish counterfeit from substandard products since according to the WHO definition, an element of intention to defraud must be ascribed to the former and this requires investigations into the sources of the suspected counterfeit products. Further, counterfeit products can have the right ingredients at the right amounts (i.e. they can pass all the

requisite tests) and will not necessarily be sub-standard, making their detection ever harder using even full laboratory investigations (WHO, 1999c).

Only SP and AQ were considered in this study because these were the first and second-line treatment for uncomplicated falciparum malaria in 2002. Although the products analysed were sampled from the private retail sector, a recent WHO multi-country study found that there were no differences in the quality of AM drugs sourced from the various public and private sector distribution chains. Public sector outlets were just as likely to have poor quality antimalarial drugs as their private sector counterparts. Table 6.7 shows Kenya specific data abstracted from this study and demonstrates that poor quality AM drugs is a general problem across all the sectors, and that for SP products, dissolution is almost always the problem, as has been shown earlier. Poor quality drugs in the government and the private sector in Kenya could be explained by the fact that the government procures drugs from the same manufacturers and importers that distribute drugs to the private sector.

Table 6.7: Percentage antimalarial products sampled from various collection points in Kenya within specifications (WHO, 2003d).

Level of collection	Chloroquine syrup	Chloroquine tablets		SP tablets	
	Content	Content	Dissolution	Content	Dissolution
Teaching hospital	1/1 (100.0%)	0/1	1/1 (100.0%)	2/2 (100.0%)	1/2 (50.0%)
District hospital	0/1	0/1	1/1 (100.0%)	2/2 (100.0%)	1/2 (50.0%)
District medical stores	2/2 (100.0%)	1/2 (50.0%)	1/2 (50.0%)	4/4 (100.0%)	0/4
Health centre	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	2/2 (100.0%)	1/2 (50.0%)
Pharmacy	2/3 (66.7%)	2/3 (66.7%)	3/3 (100.0%)	6/6 (100.0%)	3/6 (50.0%)
Vendor/shop	1/1 (100.0%)	2/3 (66.7%)	2/3 (66.7%)	8/8 (100.0%)	5/8 (62.5%)
Total	7/9 (77.8%)	6/11 (54.5%)	9/11 (81.8%)	24/24 (100.0%)	11/24 (45.8%)

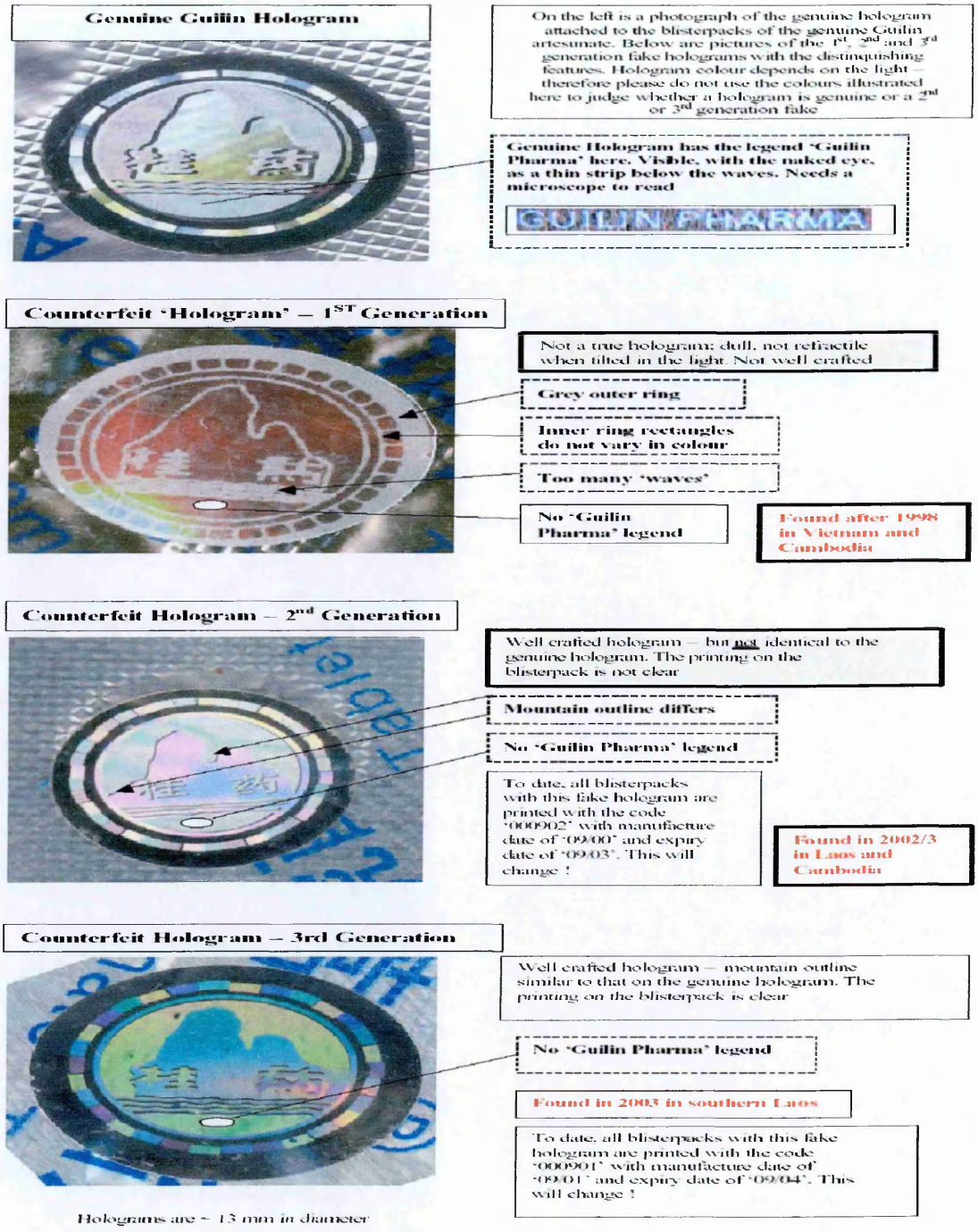
Reasons for poor quality of drugs are varied and include widespread counterfeiting (Newton *et al.*, 2001; Rozendaal, 2001), excessive decomposition of active ingredient due to high temperature and humidity (Hogerzeil *et al.*, 1991; 1992), poor storage conditions (Kibwage & Ondari, 1988; Kibwage *et al.*, 1991; 1992) and poor quality assurance during manufacture (Kibwage *et al.*, 1991; 1992; Aluoch-Orwa *et al.*, 1995; Shakoor *et al.*, 1997; Kibwage, 1998; Kibwage & Ngugi, 2000; Kinyawa *et al.*, 2000). Weak legislation and regulatory mechanisms also contribute to poor quality of drugs (Roy, 1994; Siringi, 2001).

In the case of malaria, a poor quality drug increases the risks of therapeutic failure even when the parasites are fully sensitive to the ingested compounds. This is because most drug failures are due to lower contents or dissolution scores, which is comparable to taking low doses of the drug. Sub-therapeutic drug levels could in turn lead to selection of drug resistant strains of *Plasmodium falciparum* with resistance soon spreading to the rest of the parasite population (Taylor *et al.*, 1995). The widespread resistance to pyrimethamine, and the fact that most SP samples which fail, do so with respect to the pyrimethamine component, is probably not a coincidence. The problem of poor quality drugs is compounded by the fact that most people self-treat minor ailments using drugs obtained from the retail sector (Sections 1.8 and 2.5.1), such drugs are used inappropriately (Deming *et al.*, 1989; Massele *et al.*, 1993; Slutsker *et al.*, 1994; Marsh *et al.*, 1999) and mechanisms to regulate drug use are weak or non-existent (WHO, 1999a). Given the fact that the range of affordable AM drugs is limited, the impact of poor quality on the "Useful Therapeutic Life" (UTL) of AM drugs needs urgent attention.

6.5.3 Visual inspection

Although the results of the visual inspection were inconclusive, this method has proved to be very useful in identifying fake and substandard AM products in Southeast Asia. Newton *et al.* (2001) compared the results of a simple dye test with those obtained through visual inspection of artesunate samples by an independent evaluator blinded to the results of the chemical tests. The authors found that price, quality of printing, and that of the holograms reliably predicted fake artesunate. Figure 6.3 shows genuine Guilin Pharma (China) artesunate beside first, second and third generation fake artesunate in circulation in Southeast Asia. First generation fake artesunate found in Lao and Cambodia in 1998 were poorly designed. They had a dull (as opposed to refractile) hologram and did not have the genuine 'Guilin Pharma' legend. Subsequent attempts at counterfeiting have been more sophisticated; second generation holograms were well crafted, they however had a different expiry, manufacture dates, and still did not have the 'Guilin Pharma' legend; third generation holograms were very identical to the genuine one, they had better printing, but still did not have the 'Guilin Pharma' legend (Figure 6.3). The use of cheap, visual inspection techniques to evaluate drug quality have therefore been very useful in Southeast Asia and need to be evaluated better in resource-constrained settings like Kenya.

Figure 6.3: Genuine Guilin Pharma artesunate against three generations of fake artesunate in Southeast Asia (Dr P Newton, personal communication).



6.5.4 Implications for ART-LUM

ART-LUM, the new first-line AM policy since April 2004 in Kenya, is a single-source, high value product, manufactured by a reputable international company (Novartis Pharma AG) to GMP. Therefore, sub-standard ART-LUM is unlikely to be a problem in the market. However, as is common with such high-value products, unscrupulous businessmen eager for quick profits are likely to counterfeit it. There is need to strengthen post-marketing surveillance of products in the market to identify sub-standard and counterfeit AM drugs in the market and to deal appropriately with such practices. The observation that the median remaining shelf life of artemisinin products in the private sector (12 months) was lower than for other drugs means that drug distribution mechanisms in the Kenyan public sector (historically less efficient than the private sector) need to be strengthened to avoid expiry and drug wastages (ART-LUM has short shelf life of 24 months and because of the hydrophilic nature of artemisinins, this applies to all ACTs (Dr W Muiruri, personal communication). In addition, those in the private sector need to be inspected regularly and informed clearly about shelve lives of AM drugs and be encouraged to remove expired products from their shelves.

6.6 Summary

This chapter sought to answer two questions in the light of reports of poor quality drugs in Kenya. Is there a problem with the quality of AM drugs in Kenya? and if so what is the extent of the problem? Most SP and AQ products sampled could not be said to be counterfeit according to the WHO definition, but there have been reports of counterfeit artesunate in Southeast Asia (Newton *et al.*, 2001) and of other drugs elsewhere in Africa (Section 1.9). It is possible that counterfeiting for SP and AQ was not much of a problem in Kenya because these are low value products. However, this could change with the new first-line policy, ART-LUM, which costs at least 10 times that of SP and has been adopted

by tens of governments in Africa as first-line AM drug for uncomplicated malaria (Section 1.7.4). Results also show that there is a problem with the quality of first and second line AM drugs in the market and that a third to a half of the products in circulation are substandard. A substantial proportion of these products marginally failed (mainly by being below) the pharmacopoeial specifications, probably because of poor quality control during manufacture. This reflects the fact that most developing countries including Kenya have limited regulatory mechanisms for enforcing Good Manufacturing Practices (GMP) and generally have poor or non-functional post-marketing surveillance systems. Since most drugs are imported from abroad, there is a need to improve controls at ports of entry using cheap, semi-quantitative techniques like the Mini-Lab™. However, reports of poor quality drugs need to be tempered with common sense. Communities in Kenya differ in their drug use patterns (Section 4.4.5); therefore, different poor quality drugs will have different impacts on public health. A poor quality drug whose use is minimal will not have the same public health impact as one whose use is widespread. The relationship between drug quality, adherence to dosage regimen, clinical efficacy, and drug effectiveness will be explored in more detail in the next chapter.

CHAPTER 7:

The difference between effectiveness and efficacy of anti-malarial drugs in Kenya

7.1 Introduction

Efficacy refers to how an intervention works under optimum conditions whereas effectiveness refers to how an intervention works under real-world conditions. In an efficacy trial, the intervention is delivered in a uniform manner to a specific, narrowly defined target population so that any positive or negative results can be directly attributed to the intervention. On the other hand, the goal of effectiveness trials is to investigate how interventions work under routine operational conditions among a broadly defined target population. Poor effectiveness results might therefore be attributed to lack of proper implementation or weak acceptance or adherence by participants rather than any reduced efficacy (Glasgow *et al.*, 2003).

A number of studies have tried to make a clear distinction between efficacy and community effectiveness (Tanner *et al.*, 1993; Lengeler & Snow, 1996; Krause & Sauerborn, 2000) and generally follow the principals of community effectiveness defined by Tugwell *et al.* (1985). In their seminal article, Tugwell *et al.* (1985) showed how a simple multiplicative model could be used to evaluate community effectiveness of drugs used in the management of hypertension or hip replacement in osteoarthritis. In both cases, community effectiveness was much lower than predicted from carefully controlled efficacy trials (Table 7.1). This same concept has been replicated by other workers in the evaluation of the effectiveness of insecticide treated bed nets (Lengeler & Snow, 1996), malaria treatment practices (Krause & Sauerborn, 2000) and overall effectiveness of disease control tools (Tanner *et al.*, 1993).

Table 7.1: Sample calculations for community effectiveness (Tugwell *et al.*, 1985)

Example	Efficacy	Diagnostic accuracy	Provider compliance	Patient compliance	Coverage	Community effectiveness
Hypertension						
a) Under current conditions	76%	95%	66%	65%	90%	28%
b) Under improved patient and provider compliance	76%	95%	90%	90%	90%	53%
Osteoarthritis						
a) Under current conditions	60%	75%	98%	87%	70%	27%
b) Under conditions of improved diagnostic accuracy and coverage	60%	90%	98%	87%	90%	41%

In much of sub-Saharan Africa, changes in antimalarial (AM) drug policy are largely driven by evidence from comparative clinical efficacy studies (in which treatment is directly observed). This is certainly true for the East African countries of Kenya, Uganda, Tanzania, Burundi and Rwanda under the auspices of EANMAT (Section 2.6.1). Clinical efficacy studies are performed under controlled environments with quality-assured antimalarial (AM) drugs and supervised dosing. In sharp contrast, the treatment of childhood fevers in Kenya is often undertaken at home (without professional supervision) using combinations of antipyretic (AP) and AM drugs (mostly obtained from the retail sector) (Section 1.8): 49% and 30% of fevers among children under five in the study districts were first treated with AP and AM drugs , respectively (Section 4.3.5). Such drugs can be of poor quality (41% of SP and AQ brands, Section 6.4.3) and used inappropriately (Marsh *et al.*, 1999; Okonkwo *et al.*, 2001; Yeboah-Antwi *et al.*, 2001; Nshakira *et al.*, 2002). In this chapter, a number of critical factors that are likely to influence clinical efficacy under operational conditions are explored. In addition, a quantifiable model of drug effectiveness is proposed, based on the nationally recommended first and second line drugs in Kenya at the time of the surveys (2001 to 2003). The implications for the new first-line AM drug, ART-LUM are also discussed.

7.2 Materials and methods

7.2.1 Study sites

This chapter uses combinations of drug efficacy data (Section 2.6.2), drug access/use (Section 4.3.5), drug quality (Section 6.4.3), and adherence from the four surveyed districts described in detail in Section 4.2.1.

7.2.2 Estimation of effectiveness

The effectiveness of SP and AQ was estimated from three variables: adherence to recommended dose regimen, drug quality, and clinical efficacy. The present thesis did not attempt to define adherence, as these methods were too complex for the rapid community survey. Rather, estimates of adherence to SP and AQ dose regimens in Kenya were obtained through detailed household surveys of treatment seeking behaviour for recent fevers among children under 5 years in two districts during 2003 (Makueni and Kwale), undertaken by Dr. V. Marsh and colleagues (unpublished data). Detailed information was collected on the management of recent fevers from a two stage, randomised cluster sample of 4000 households from four suitable rural divisions in each district. Approximately 20 randomly selected clusters of households, where each cluster contained an average of 100 households, were used.

Reported over-the-counter (OTC) drug use information was collected in local languages using a structured questionnaire and samples of tablets and packaging of locally available brands to support drug identification. Where available, remaining tablets, syrup bottles or packaging were inspected. A supervisor repeated ten per cent of all antimalarial drug use interviews. Concordance between first and second interviews supported the accuracy of reporting by eliminating recording errors and minimising recall bias. Information was collected on the total amount of a specified antimalarial drug given, the number of days of

administration and the age of the child. Treatments were coded as 'adequate', 'high dose' or 'low dose' by comparison with national standard treatment guidelines (DOMC, 1998). For the present analysis, patients who took a higher dose than recommended and those who took an adequate dose were combined into a single group labelled 'adequate adherence'. Whereas a high dose would conceivably lead to higher incidence of side effects or toxicity, it would still give maximum clinical efficacy; in this regard therefore, this group is no different from the adequate dose group.

Data on the quality of SP and AQ products are described in detail in Chapter 6. These data were refined for the present analysis such that in addition to classifying products as having passed or failed the pharmacopoeial tests, a quality index (ranging from 0 to 1) was derived by multiplying results of content and dissolution tests performed on test batches. Products with content or dissolution greater than 1 (those with content and/or dissolution more than label claim) were given the highest possible score of 1. Suspensions were given an ideal dissolution score of 1. For each of the drug classes SP, AQ, and each product i the quality index Q was expressed as:

$Q_i = D_i C_i$, where D and C are the dissolution and content scores, respectively.

Where more than one batch of a product was tested, mean proportionate content was multiplied by mean proportionate dissolution. Where no quality tests were conducted for a given product, averaging other products for which results were available derived an approximate quality index. In earlier published work (Amin *et al.*, 2004), a quality index of 1 was assumed for products obtained from the formal sector. In Kenya, drug supply to government health facilities is predominantly through an essential drugs kit system. Supply usually follows award of a tender handled through an independent procurement agency.

Tenders are usually awarded based on, among other things, good quality as judged on submitted samples, thus a quality index of 1 for such products seemed plausible. The Mission and NGO facilities also use a similar centralized drug procurement system and might differ only as far as disbursement to the facilities is concerned (Section 3.3.1). As has been shown in Section 6.5.1, however, there is no difference in the quality of drugs accessed from the private retail sector or the government sector in Kenya. As such, quality indices for SP and AQ reportedly obtained from the public sector (marked "formal" in the tables) have been revised to those of the most likely supplier to this sector, i.e. Cosmos Limited, Kenya (Crown Agents, personal communication). For SP "formal', a quality index equivalent to that of Falcidin® (0.854) has been assumed and for AQ "formal", a quality index equivalent to Malaratab® (0.751) has been assumed.

Thirdly, the proportionate use of SP and AQ was determined by a community survey of childhood fever treatment practices conducted in the same districts in 2001 and described previously (Section 4.2.3). Finally, estimates of clinical efficacy were derived from national surveillance data of SP and AQ monotherapy undertaken within the four sentinel districts (http://www.eanmat.org, accessed 28/08/04) from January 2000 to February 2003. There have been changes in the definitions of efficacy of AM drugs overtime, as such the effectiveness of SP and AQ are presented bearing in mind these definitions (Section 1.7.3).

The predicted effectiveness of SP and AQ was estimated from (a) adherence to dose regimen, (b) quality of products used (weighted for proportionate use in the community and considering sectoral variation in quality) and (c) clinical efficacy, using the equation:

$$E = eA\sum_{i=1}^{i=n} Q_i U_i$$

Where: E=Effectiveness, e=efficacy, A=Adherence, n=number of products, i=given product i, Q=quality index, and U=proportionate product use. The term $\sum_{i=1}^{i=n} Q_i U_i$ defines the use-weighted quality index.

7.2.3 Parameter uncertainty

To explore the impact of parameter uncertainty on the effectiveness estimates, a best- and worst-case scenario analysis was conducted. Estimates for e, A, Q and U in the equation were substituted by values representing a plausible range for the point estimates (Drummond *et al.*, 1997). Plausible ranges for e were determined by considering the maximum and minimum value for clinical efficacy from the various studies in the study districts. In some cases, these ranges painted a rather rosy picture of clinical efficacy in the sentinel districts and were contradicted by data from non-EANMAT sources (Section 2.6.2). For instance, the worst Day 14 ACPR for AQ was reported by AMREF as 61.3% in Mwea (Table 2.5), yet the EANMAT minimum value was 84% (Table 7.1). In such cases, non-EANMAT min-max ranges were used in the sensitivity analysis.

Plausible ranges for adherence to AQ were not available from the literature, thus those for chloroquine (CQ), a close congener, were used. The worst reported adherence to a three-day regimen for CQ (2.8%) was in Kilifi, Kenya (Marsh *et al.*, 1999). This was rounded off to the nearest probability of 10%. The best was reported by Yeboah-Antwi *et al.* (2001) in Ghana at 49.8% (rounded off to approximate probability of 50%). Adherence to SP was varied from 50 to 80%. Estimates for Q and U are derived from the survey data since there were no comparators in the literature, use-adjusted quality index (QU) was varied from 70 to 90% for both SP and AQ since their derived QU indices were similar. Efficacy estimates for the non-adherent group (and plausible ranges) were intuitively derived on the assumption that they would be lower than the lower value of the plausible range for the

adherent group. In the sensitivity analysis, these figures were altered to the same magnitude as the adequate adherence group.

7.3 Results

Table 7.2 shows the clinical efficacy (e) of SP and AQ derived from national surveillance data between January 2000 and February 2003. For AQ, Day 14 ACR was estimated to be 95.8% (84.0 to 100.0%) across nine studies in the four districts and for SP it was estimated to be 80.1% (48.4 to 100.0%) from a similar number of studies in the four districts. Day 14 ACPR for AQ was 95.2% (84.0 to 100.0) and that for SP was 74.1% (45.2 to 96.8). Day 28 ACR for AQ and SP was 95.1% (91.6 to 99.1) and 80.2% (70.4 to 91.6), respectively. Using the new WHO definition, Day 28 ACPR of AQ was estimated at 77.7% (69.0 to 87.0) and that of SP at 72.0% (62.5 to 83.1). As has been explained in Section 7.2.3, the lower ranges of Day 14 AQ clinical efficacy were revised (to 80.7 to 100.0% ACR and 61.3 to 100.0% ACPR, respectively) to take into account non-EANMAT data that showed worse clinical efficacy of AQ; the EANMAT SP ranges shown included worst and best-case clinical efficacy reported by non-EANMAT sources and so there was no need to adjust these.

Table 7.2: Summary of EANMAT drug efficacy studies (9 SP and 9 AQ) in four sentinel sites in Kenya between January 2000 and February 2003 (http://www.eanmat.org, accessed 28/08/04)

	Patients completing follow-up	ACR* (old definition)	ACPR† (new definition)
AQ day 14 outcomes	593	95.8% (80.7‡-100.0)	95.2% (61.3‡-100)
AQ day 28 outcomes	340	95.1% (91.6-99.1)	77.7% (69.0-87.0)
SP day 14 outcomes	528	80.1% (48.4-100)	74.1% (45.2-96.8)
SP day 28 outcomes	291	80.2% (70.4-91.6)	72.0% (62.5-83.1)

* ACR (Adequate clinical response)- achieved if there is no parasitaemia or no fever on Day 14 without previously meeting the criteria for ETF or LTF (WHO, 1996)
†ACPR (Adequate Clinical and Parasitological Response)-absence of parasitaemia on Day 14 (or Day 28), irrespective of axillary temperature, without previously meeting any of the criteria for ETF, LTF or LPF (WHO, 2003a)
‡ Lower range from AMREF data (Table 2.5)

Table 7.3 shows the quality assurance and frequency of use data for SP products. Table 7.4 presents the same frequencies for AQ. Use-weighted quality indices were computed for SP and AQ from results in these tables as described in the methods section. These were estimated to be 83.1% and 83.8% for SP and AQ, respectively.

Table 7.3: Results of SP products analysed in 2002 and their respective proportionate use in four communities in Kenya.

Product (i)	Number (of total) batches passing content and/or dissolution	Quality index (Q)	Product proportionate use in the community (U)
SP tablets			
Amalar®	2/2	0.912	0.007
Falcidin®	4/4	0.854	0.033
Falcigo®	0/1	0.642	0.000
Falcistat®	nt	0.750*	0.003
Fanlar®	2/2	0.868	0.000
Fansidar®	4/4	0.809	0.664
Fansimax®	0/1	0.672	0.000
Intadoxin®	0/1	0.484	0.010
Laridox®	1/1	0.933	0.000
Malareich®	3/3	0.899	0.000
Malastin®	0/1	0.682	0.000
Malidar®	0/2	0.588	0.000
Malodar®	3/3	0.785	0.000
Malostat®	0/1	0.763	0.000
Methomine-S®	0/1	0.517	0.000
Nopyrin®	1/1	0.678	0.016
Orodar®	2/2	0.864	0.026
Pyralfin®	1/1	0.994	0.003
Unidar®	1/3	0.548	0.007
Viparum®	0/3	0.566	0.000
SP unspecified formal†	nt	0.854	0.046
SP unspecified retail‡	nt	0.750*	0.030
Sub-Total 1	**24/37**		**0.845**
SP suspensions			
Falcidin®	3/4	0.988	0.053
Falcigo®	0/3	0.918	0.016
Falcimax®	0/3	0.905	0.000
Fansimax®	1/1	1.000	0.000
Intadoxin®	1/3	0.957	0.003
Lansidar®	1/2	0.931	0.000
Malidar®	0/2	0.841	0.000
Medifan®	2/2	0.977	0.036
Nopyrin®	0/1	0.919	0.010
Orodar®	1/2	0.909	0.000
Pyralfin®	1/2	0.962	0.030
Unidar®	1/2	0.995	0.000
Viparum®	nt	0.950*	0.007
Sub-Total 2	11/27		0.155
SP Total	33/64		1.000

SP-sulfadoxine-pyrimethamine. nt-not tested. Product (i)-tablet or paediatric suspension. Batch-unique identifier given to a product by manufacturer. Quality index (Q)-product of content and dissolution tests. For suspensions, only content test done *Quality index estimated from the average quality index of the other products in the category. Community use index (U)-number of encounters with product as proportion of total in the class. †Formal-drug obtained from government, Mission, or NGO sector and given quality index of Falcidin®. ‡Retail-drug obtained from outside formal sector.

Table 7.4: Results of AQ products analysed in 2002 and their respective proportionate use in four communities in Kenya.

Product (i)	Number (of total) batches passing content and/or dissolution	Quality index (Q)	Product proportionate use in the community (U)
AQ tablets			
Alphaquine®	1/1	0.766	0.000
Amobin®	3/3	0.897	0.087
Amoquin®	nt	0.800*	0.091
Amowin®	1/1	0.850	0.000
Betaquine®	2/4	0.432	0.033
Camoquin®	3/4	0.845	0.043
Diaquin®	1/1	0.898	0.000
Emoquin®	2/3	0.763	0.000
Kamoc®	2/2	0.914	0.000
Laeoquin®	1/2	0.691	0.000
Malaratab®	2/6	0.751	0.243
Uniquin®	2/2	0.879	0.004
AQ unspecified formal†	nt	0.751	0.018
AQ unspecified retail‡	nt	0.800*	0.014
Sub-Total 1	**20/29**		**0.533**
AQ suspensions			
Amobin®	1/4	0.845	0.214
Amoquin®	1/1	0.947	0.000
Camoquin®	3/3	1.000	0.058
Emoquin®	1/2	0.933	0.033
Falciquin®	3/3	0.966	0.040
Kamoc®	0/1	0.827	0.000
Laeoquin®	0/1	0.618	0.000
Malarabit®	1/1	0.956	0.000
Malaramed®	3/4	0.960	0.004
Malaratab®	2/2	0.960	0.105
Uniquin®	1/1	0.998	0.014
Sub-Total 2	**16/23**		**0.467**
AQ Total	36/52		1.000

AQ-amodiaquine. nt-not tested. Product (i)-tablet or paediatric suspension. Batch-unique identifier given to a product by manufacturer. Quality index (Q)-product of content and dissolution tests. For suspensions, only content test done. *Quality index estimated from the average quality index of the other products in the category. Community use index (U)-number of encounters with product as proportion of total in the class. †Formal-drug obtained from government, Mission, or NGO sector and given quality index of Malaratab®. ‡Retail-drug obtained from outside formal sector.

Table 7.5 shows adherence (**A**) to SP and AQ in Kwale and Makueni. 66.7% of patients on SP and 13.8% of those on AQ were considered as having "adequately adhered" (correct dose for correct duration). Table 7.6 summarises the results of Tables 7.2 to 7.5 to derive overall effectiveness estimates for SP and AQ according to the various definitions. Using the latest WHO definition of clinical efficacy (Day 28 ACPR), a point estimate for effectiveness of 51% was obtained for SP, with worst/best case estimates of 28 to 70% thus:

Point estimate:

[0.667*0.720*0.831] + [0.333*0.4*0.831] = 0.510 or 51%

Worst estimate:

[0.5*0.6*0.7] + [0.5*0.2*0.7] = 0.28 or 28%

Best estimate:

[0.8*0.8*0.9] + [0.2*0.7*0.9] = 0.702 or 70%.

Likewise, overall effectiveness of AQ was estimated to be 45% (29 to 68%). The observed differences between adherence to one-day versus three-day regimen (66.7% versus 13.8%) would probably account for most of the differences between the estimated effectiveness of AQ and SP in Kenya.

Table 7.5: Adherence (A) to recommended dose regimen for children under 5 years using OTC SP and AQ drugs for a recent fever in Kwale and Makueni districts (2002-3)

	SP		AQ	
	Adequate* or High dose	**Low dose**	**Adequate* or High dose**	**Low dose**
Kwale	29/46 (63.0%)†	17/46 (37.0%)	10/60 (16.7%)	50/60 (83.3%)
Makueni	23/32 (71.9%)	9/32 (28.1%)	3/34 (8.8%)	31/34 (91.2%)
Total	52/78 (66.7%)	26/78 (33.3%)	13/94 (13.8%)	81/94 (86.2%)

* Adequate dose for age, based on national standard treatment guidelines. High dose/Low dose implies higher or lower than those on guidelines.
† Values in parentheses represent proportions in each category

Table 7.6: Effectiveness versus efficacy of SP and AQ in Kenya.

		Adequate adherence group*	Inadequate adherence group†
SP	Estimated efficacy day 14 ACR (A)	0.801 (0.5-1.0)‡	0.4 (0.2-0.7)‡
	Estimated efficacy day 28 ACR (B)	0.802 (0.7-0.9)‡	0.4 (0.2-0.7)‡
	Estimated efficacy day 14 ACPR (C)	0.741 (0.5-1.0)‡	0.4 (0.2-0.7)‡
	Estimated efficacy day 28 ACPR (D)	0.720 (0.6-0.8)‡	0.4 (0.2-0.7)‡
	Use-weighted quality	0.831 (0.7-0.9)‡	0.831 (0.7-0.9)‡
	Proportion of patients	0.667 (0.5-0.8)‡	0.333 (0.5-0.2)‡
Overall SP effectiveness (A)	0.55 (0.25-0.85)§		
Overall SP effectiveness (B)	0.56 (0.32-0.77)§		
Overall SP effectiveness (C)	0.52 (0.25-0.85)§		
Overall SP effectiveness (D)	0.51 (0.28-0.70)§		
AQ	Estimated efficacy day 14 ACR (A)	0.958 (0.8-1.0)‡	0.5 (0.4-0.6)‡
	Estimated efficacy day 28 ACR (B)	0.951 (0.9-1.0)‡	0.5 (0.4-0.6)‡
	Estimated efficacy day 14 ACPR (C)	0.952 (0.6-1.0)‡	0.5 (0.4-0.6)‡
	Estimated efficacy day 28 ACPR (D)	0.777 (0.6-0.9)‡	0.5 (0.4-0.6)‡
	Use-weighted quality	0.838 (0.7-0.9)‡	0.838 (0.7-0.9)‡
	Proportion of patients	0.138 (0.1-0.5)‡	0.862 (0.9-0.5)‡
Overall AQ effectiveness (A)	0. 47 (0.32-0.72)§		
Overall AQ effectiveness (B)	0.47 (0.32-0.72)§		
Overall AQ effectiveness (C)	0.47 (0.29-0.72)§		
Overall AQ effectiveness (D)	0.45 (0.29-0.68)§		

* Took adequate dose or higher than adequate according to the standard treatment guidelines (STGs)
† Took lower dose than recommended by STGs
‡ Estimated plausible ranges for parameters
§ Point/base estimate; in brackets worst/best estimate

7.4 Discussion

In this chapter, combinations of clinical efficacy, quality and adherence to first and second line AM drugs available in Kenya have been examined using empirical observations from four districts. Analysis of these composite data suggest that despite a clinical efficacy of over 72% for SP (ACPR on Day 28) in government clinics during the period of observation, SP effectiveness may be as low as 51% under common usage patterns. Likewise, the effectiveness of AQ might be as low as 45% compared to a clinical efficacy of 78%.

7.4.1 Need to weight quality by use

Quality assurance of AM drugs in developing countries is usually sporadic. Products in circulation are rarely sampled for quality checks because of institutional or financial constraints (Chapter 3). Therefore, linking use and distribution to quality assurance would be a practicable way to focus on the small number of AM drugs that are critical to the community at any one time. In the parsimonious model suggested in this chapter, drug quality was adjusted by community use to arrive at a use-weighted quality index. This takes into consideration the relative importance of the various products, i.e. how often they are used. For example, although the quality indices for most SP suspensions were well over 90%, SP suspensions were reportedly used in only 16% of cases where SP was the drug of choice. Conversely (and intuitively), a sub-standard but widely used product is of greater public health concern.

7.4.2 Study limitations

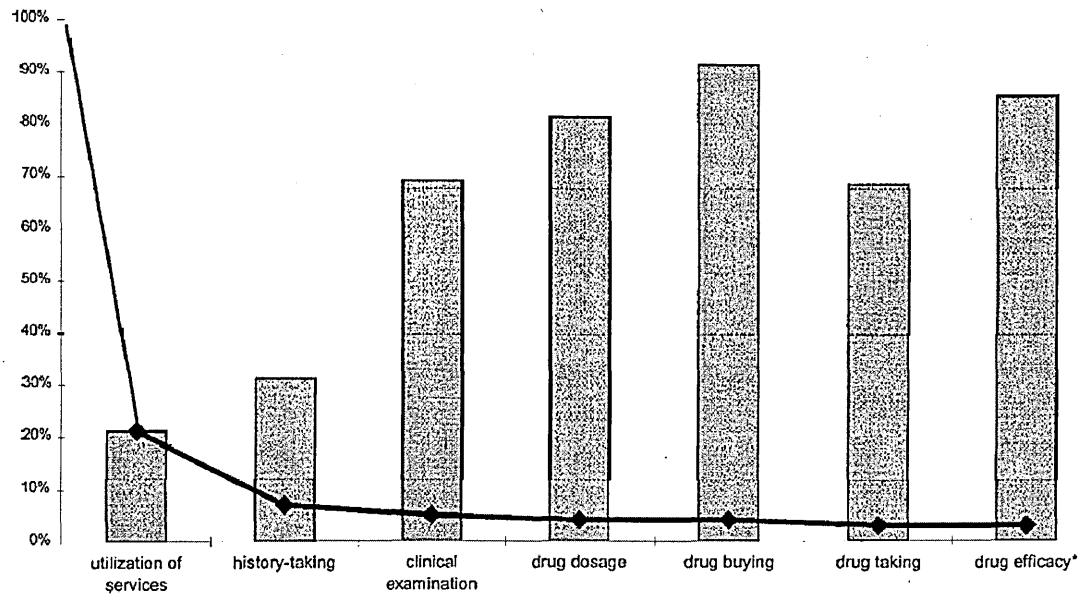
This simple model has a number of limitations. First, it was assumed that there is a linear relationship between and within the various parameters. In reality, this might not always be true as the dose(adherence)-response relationships are typically sigmoidal. Secondly, data

on adherence were limited to only two of the study sites. However, observations are consistent with the very few other carefully conducted studies of adherence (Marsh *et al.*, 1999; Okonkwo *et al.*, 2001; Yeboah-Antwi *et al.*, 2001; Nshakira *et al.*, 2002) which suggest that three day regimens are poorly adhered to under routine conditions with 2.8% (Marsh *et al.*, 1999) to 49.8% (Yeboah-Antwi *et al.*, 2001) of patients taking the correct dose for the appropriate duration. Given a high quality, highly efficacious drug, adherence would probably be the single biggest impediment to drug effectiveness and may reduce efficacy to true effectiveness by as much as 40%. However, there is a need to model pharmacodynamics of drugs against their adherence since some drugs are know to be "forgiving", i.e. they give a favourable response even among the poorly adhering (Urquhart, 1998; Hughes & Walley, 2003). Adherence to dosage regimen is especially important in the light of artemisinin-based combination therapies like ART-LUM, which have a complex dosing regimen and whose effectiveness could potentially be compromised by poor adherence.

A third limitation of this model is its scope. A more elaborate model has been used by Krause and Sauerborn (2000) in Burkina Faso in calculating community effectiveness of malaria treatment. In this model, seven steps were considered to be essential in malaria treatment: a) utilisation of health services; b) completeness of history taking; c) completeness of clinical examination; d) prescription of correct dosage of antimalarial drugs; e) buying correct amount of drug by patients; f) compliance in drug taking; and g) clinical efficacy of the antimalarial drugs. From these parameters, the authors concluded that the effectiveness of malaria treatment using CQ in Burkina Faso was approximately 3% in 2000 (Figure 7.1). Although the broad principles of Krause and Sauerborn's model were used for the present study, the proposed model was pared down to a few, salient parameters. This was because a) drug effectiveness was considered to be a function of

adherence, quality and clinical efficacy for patients who had reported access to a given drug; and b) elements of quality of care of different providers was not possible to estimate accurately and for all sectors from which drugs were accessed in Kenya. Further, a consideration of these two factors would require expansion of the present work to that of performance of the Kenyan health sector in delivering antimalarial services to patients and would therefore be outside the scope of the present study.

Figure 7.1: Proportion of effective procedures (in % columns) and estimated effectiveness (in % lines) of seven steps in the process of treating malaria (Krause & Sauerborn, 2000).



7.4.3 Plausible ranges

Plausible ranges were assigned to account for uncertainty. In some models, the 95% confidence interval around the point estimate is used as the plausible range. This was not possible for all of the parameters of the model in this chapter since some parameters were derived and did not exist in literature (e.g. the quality and use-weighted quality indices). Moreover, as the uncertainty around the estimate of effectiveness is the product of each

individual uncertainty estimate, focusing on details with some parameters, when no data existed for the remainder seemed counterproductive.

7.4.4 Projected effectiveness of ART-LUM, the new first-line policy

An attempt was made to estimate the effectiveness of ART-LUM, the new first-line policy in the Government of Kenya (GoK) sector in a method similar to the one described in this chapter. Since ART-LUM will be sourced from a single company (Novartis Pharma AG) and will presumably be manufactured to GMP, a quality index of 1 is plausible. Day 28 ACPR for ART-LUM in Kilifi, Kenya was estimated at 92.4% in a recent study among 92 children under five who completed follow-up (Dr M Makanga, personal communication). In the absence of other studies on ART-LUM in Kenya (to provide the minimum and maximum reported clinical efficacy as in SP and AQ), the Fleiss quadratic 95% confidence interval was used as the range for the sensitivity analysis (90.1 to 99.2%, calculated using EPI-Info version 6.0d4, Centers for Disease Control, USA). On a scale of 0 to 1, these represent approximate probabilities of 0.9 to 1.0 (or 90% to 100%).

Very few studies have been done on adherence to ACTs in Africa. In two recent studies in Zambia and in the Sudan, Deporteere *et al.* (2004a; 2004b) estimated the adherence to SP-artesunate and ART-LUM. In the Zambian study, guardians of 162 children aged five years or below with confirmed malaria in the Maheba Refugee Camp treated with SP-artesunate (SP-AS) were interviewed about use of the drug on the day following the last administered dose. Compliance was determined using the pill count method to see how many tablets or sachets were used over the treatment period and what drug remained on the day of the interview. Children were put in three categories: those who had one or more doses of the drug left (certainly non-compliant); those with no drug left and who had reported drug use according to exact instructions of the health worker (probably compliant)

and those with no drug left, but who had not used the drugs according to health worker instructions (probably non-compliant). From this study, those who were probably complaint were estimated to be 39.4% (Depoortere *et al.*, 2004a). In another study in the Sudan in 2004, using a similar methodology, the authors estimated adherence to ART-LUM as 59.1% among 93 children aged five or below (Depoortere *et al.*, 2004b).

In a study in Mbarara, Uganda, Fogg *et al.* (2004) estimated adherence to six-dose ART-LUM. Patients (all age groups) with uncomplicated malaria were given the first dose of ART-LUM then instructed on how to take the remaining five doses. A combination of pill counts and questionnaires were then used to measure adherence after doses were estimated to have been completed (day 3). Adherence was defined as in the Depoortere studies above. Among 210 patients for whom data were complete, 10% were probably or definitely non-adherent and 90% probably adherent.

In yet another study in Rufiji, Tanzania, 253 out-patients (>=2 months of age) presenting to the Ikwiriri health centre with uncomplicated malaria and who had been given SP-AS were recruited for a study on adherence. Adherence was measured at 24 and 48 hours based on self-reports and pill counts, and defined as correct dose for the day of follow up and by number of tablets completed using pill count. A composite measure for adherence was derived from these two methods; complete adherence to SP-AS was estimated to be 75% (Kachur *et al.*, 2004).

Using the average of these four estimates (65.9%) as the point estimate, and their extremes (39.1 to 90.0%) as worst- and best-case scenarios, modelled effectiveness for ART-LUM was estimated to be 85% (72 to 99%), far superior to either SP (51%, 28 to 70%) or AQ (45%, 29 to 68%). Although the estimated adherence to ART-LUM seems high for a three-

day regimen and therefore counterintuitive, there is evidence to suggest that patients are more likely to adhere to more effective drugs like ART-LUM (even three-day regimen) better than failing drugs like CQ and AQ of a similar dosage regimen (Yeung & White, 2005).

7.5 Summary

The chapter highlights the important differences between efficacy and effectiveness of widely used first and second line anti-malarial drugs under routine formal and retail sector use in Kenya. It shows that a drug's effectiveness cannot be measured reliably through *in vivo* clinical efficacy tests and factors related to brand use, brand quality and adherence should all be considered when defining replacement drugs for failing nationally recommended therapeutics. It also demonstrates that with the limited available data, the new first-line treatment, ART-LUM may prove to be more effective under operational conditions than either SP or AQ.

The data needed to populate this parsimonious model of effectiveness can be collected in the sentinel districts as part of monitoring and evaluation of the RBM investments in Kenya. Surveys are already planned to evaluate mid-point targets for 2005/2006 on fever management practices and coverage of ITNs among other process and outcome indicators (Prof RW Snow, personal communication). Existing tools on fever management practices in the districts can be improved to collect better data on adherence to the antimalarial drugs. In addition, quick preliminary analyses would give a sense of brand preference by communities and thus guide sample collection for quality control. Such data can subsequently be used to model effectiveness and might have an increased programmatic utility over routine efficacy testing of the antimalarial drugs.

CHAPTER 8:

Conclusions

8.1 Introduction

A renewed interest in the control and management of malaria has followed the launch of the Roll Back Malaria (RBM) initiative in 1998. RBM seeks to reduce malaria morbidity and mortality by 50% by 2010. In Africa, where access to clinical and laboratory facilities are limited, the main strategy for achieving this goal is prompt, presumptive treatment of fever. The retail sector in Africa plays a very important role in fever management, with fevers often first being treated with antimalarial or antipyretic drugs obtained from the retail sector (Section 1.8.1.2 and 4.4.3). Rather than alienate this sector, the Kenyan Government has embarked on targeted training programmes to enhance service delivery (Section 5.4.3). Training programmes, however, will achieve little public health value if drugs in the retail sector are sub-standard or counterfeit (Section 6.4.3), and if relevant regulatory mechanisms and legislation are wanting (Section 3.4.3). Sub-standard and counterfeit drugs are a hindrance to the effectiveness of strategies promoting home-based care.

8.2 Summary of key findings

The thesis addressed three broad themes: measuring the extent of prompt access to antimalarial drugs; modelling drug effectiveness under operational conditions allowing for sub-standard products and adherence; and lastly the policy environment under which drugs are regulated. These were put in the context of antimalarial drug policy changes in Kenya. The key findings were:

8.2.1 Access to services and to treatment

- About 39% of fevers among children under five years of age in Kenya are treated through the formal sector and 29% through the retail sector. A substantial proportion of fevers (28%) remain untreated.

- Most fevers are treated with antipyretic (49%) or antimalarial drugs (30%), a finding that is consistent with what has previously been reported by other workers in Kenya, and in Africa
- Fevers treated through the formal sector have a higher chance of receiving an antimalarial drug than those treated through other sectors (56 versus 37%)
- A waiting period of between two and three days is common before treatment is sought
- Overall, less than 3% of paediatric fevers were treated within 24 hours with SP in 2001, the first-line drug at the time of the study, against an international target of 60% fevers to be treated presumptively as malaria by 2006.

8.2.2 Drug effectiveness

- 41% of first and second-line antimalarial drugs were found to be substandard
- When differential brand use and adherence to SP and AQ were combined with drug quality, the modelled effectiveness of SP was estimated to be 51% and that of AQ to be 45%; compared with a clinical efficacy of 72% and 78% for SP and AQ, respectively
- The modelled effectiveness of ART-LUM, the proposed new first-line drug, was 85%, far better than either SP or AQ

8.2.3 Drug regulation and antimalarial drug policy changes

- About half of first and second-line drugs in Kenya are unregistered and their safety, quality, and efficacy cannot be guaranteed.
- There is no functional post-marketing surveillance system to protect the market from the trade in sub-standard and counterfeit antimalarials or to mop up failing antimalarial drugs like SP

- Antimalarial drug policy changes in Kenya are not linear, scientific processes, but cyclical, both scientific and political endeavours

8.3 Future extension and applications of effectiveness models

Chapter 7 brought together a number of parameters that are important for the effectiveness of the antimalarial drugs (quality, efficacy, adherence, and differential brand use). Here, an attempt is made to extend this to a far more important concept than drug effectiveness, that of antimalarial drug policies with the premise that effective drugs (not efficacious) are of no use to communities if they remain inaccessible to the majority of those who need them. Although not exhaustive, the few parameters used in the proposed model serve as a conceptual framework for thinking about the effectiveness of drug policies, and requires further work.

Figure 8.1 and Table 8.1 show the conceptual framework of community drug policy effectiveness and the parameter estimates used to derive preliminary figures for SP and AQ. The entry point to the model is treatment seeking for fevers. From the findings in Chapter 4, about 39% of paediatric fevers will be treated through the formal sector, 29% through the retail sector, and about 28% remain untreated. Of those seeking treatment from the formal sector, 55% will receive the first-line drug (SP in 2001-2003) and 5% AQ (Zurovac *et al.*, 2004). Conversely, for those seeking treatment through the retail sector, only 10% will receive SP and 14%, AQ (Section 4.4.3). Zurovac and colleagues' data are quoted here because, as explained in Chapter 4, mothers do not accurately recall drugs obtained from the formal sector unlike the retail sector where they purchase drugs of their choice.

The next step in the framework is the proportion of those who receive either drug and are given an adequate dose. For SP in the formal sector, about 34% will receive an adequate dose according to the national treatment guidelines, 45% higher than recommended and 22% lower than recommended (Zurovac *et al.*, 2005). For AQ, 10% will receive an adequate dose, 29% a higher than recommended and 62% lower than recommended (Zurovac *et al.*, 2002). Similar to the earlier assumption in Chapter 7, those who are prescribed an adequate or high dose will presumably derive the same benefit in terms of efficacy (hence the terms "adequate prescription", and "full efficacy"). Conversely, those who receive a lower dose will derive some benefit from the drug, thus "inadequate prescription" and "partial efficacy" in Table 8.1.

In the retail sector, the "prescription step" is missing from the conceptual framework because clients' have a choice on what to buy or not to buy depending on their ability and willingness to pay. It therefore means that adherence patterns for drugs obtained from the retail sector are actually composite figures of a) what is bought (adequate, over- or under-dose), and b) how what is bought is used, thus obviating the prescription step in the formal sector. Likewise, for the adherence parameter (again in the manner of Chapter 7), about 67% of those who obtain SP from the retail sector "adequately adhere" and 14% of those who purchase AQ adequately adhere. These two groups have been assumed to derive "full efficacy" from the drugs, while those who inadequately adhere, have been assumed to derive partial benefit, thus "partial efficacy" in Table 8.1, i.e. adherence is not an all or none scenario but a continuum (the same assumption was made for drug quality by way of the quality index in Chapter 7).

The third step is at the level of the drug. Different brands will be accessed from the different sectors and the preference for these brands will differ, thus the need to weight

quality with use. The use-weighted quality indices for SP were similar in both sectors, i.e. both were 83%; that for AQ was marginally higher in the formal sector (85%) than in the retail sector (81%).

Figure 8.1: A conceptual framework of community effectiveness of antimalarial drug policies

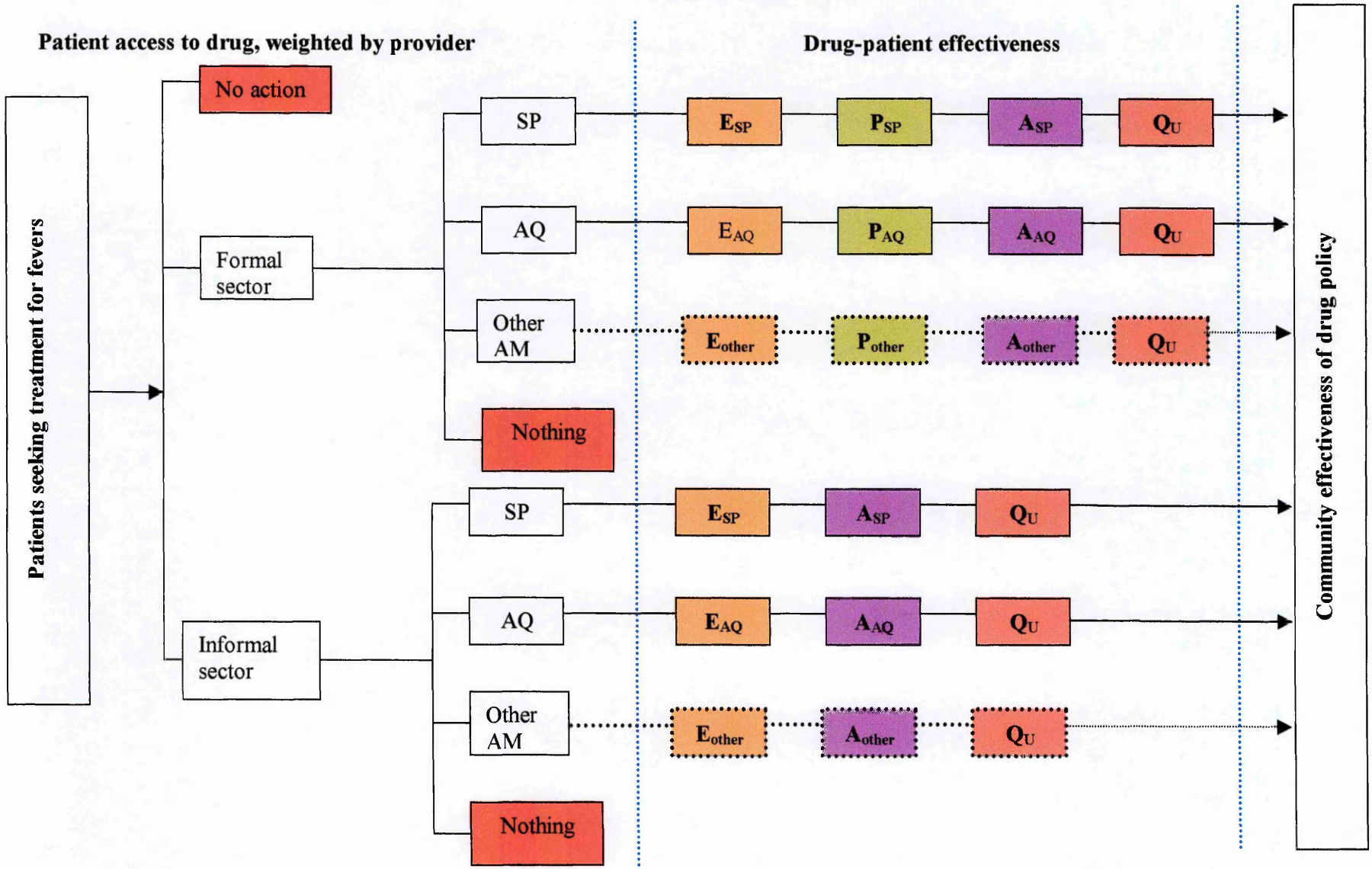


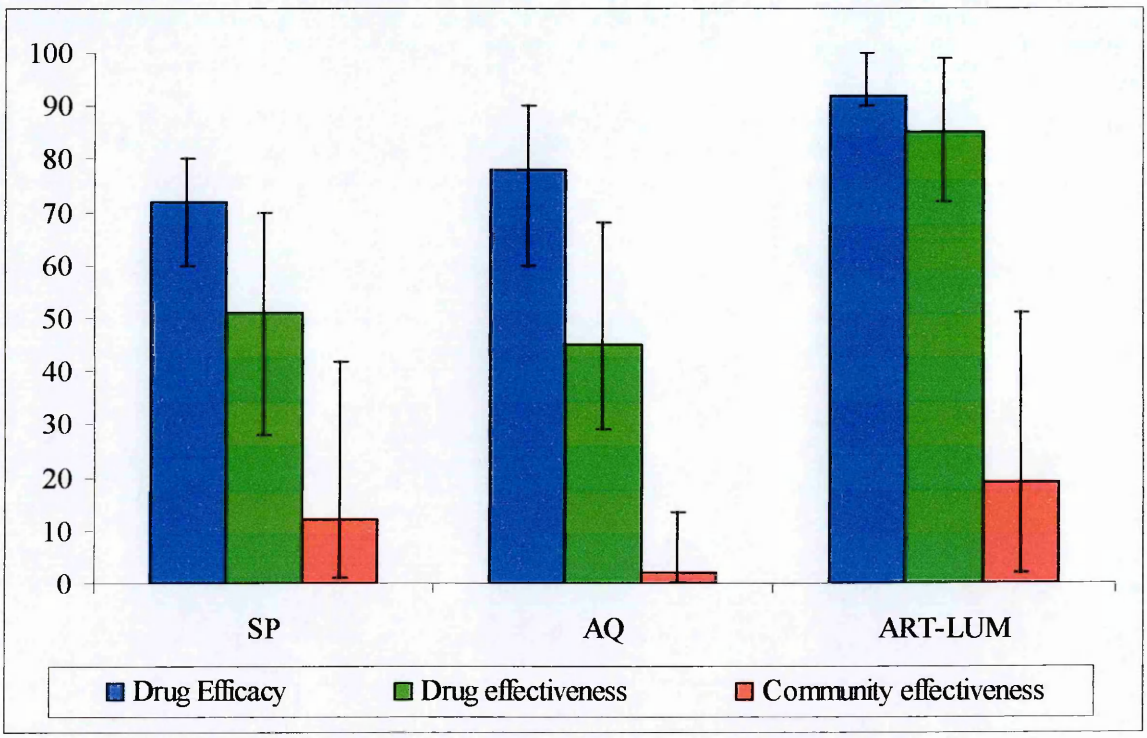
Table 8.1: Parameters used to populate an example community effectiveness model for sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ)

	Parameter	Point estimate (plausible range)*	Reference
No action	Fevers where no action was taken	na[†]	na
Formal sector[‡]	Fevers accessing the formal sector	39.1% (5 to 83%)	Table 4.6 (Figure 2.5)
Retail sector[§]	Fevers accessing the retail sector	29.2% (11 to 77%)	Table 4.6 (Figure 2.6)
SP	Fevers treated with AQ in:		
	Formal sector	55.3% (52.3 to 58.3%)	Zurovac *et al.* (2004) (95% CI)[‖]
	Retail sector	9.5% (7.6 to 11.9%)	Table 4.12 (95% CI)
AQ	Fevers treated with AQ in:		
	Formal sector	5.1% (3.8 to 6.6%)	Zurovac *et al.* (2004) (95% CI)
	Retail sector	13.8% (11.5 to 16.5%)	Table 4.12 (95% CI)
E_{SP}	Full efficacy of SP	72.0% (60.0 to 80.0%)	Table 7.6
	Partial efficacy for SP	40.0% (20.0 to 70.0%)	
E_{AQ}	Full efficacy of AQ	77.7% (60.0 to 90.0 %)	Table 7.6
	Partial efficacy of AQ	50.0% (40.0 to 60.0%)	
P_{SP}	"Adequate prescription[¶]" of SP	78.5% (75.7 to 81.4%)	Zurovac *et al.* (2005) (95% CI)
	"Inadequate prescription" of SP	21.5% (18.6 to 24.3%)	
P_{AQ}	"Adequate prescription" of AQ	38.4% (29.6 to 47.9%)	Zurovac *et al.* (2002) (95% CI)
	"Inadequate prescription" of AQ	61.6% (52.1 to 70.4%)	
A_{SP}	"Adequate adherence[**]" to SP	66.7 (50.0 to 80.0%)	Table 7.6
	"Inadequate adherence" to SP	33.3% (20.0 to 50.0%)	
A_{AQ}	"Adequate adherence" to AQ	13.8% (10.0 to 50.0%)	Table 7.6
	Inadequate adherence to AQ	86.2% (50.0 to 90%)	
Q_U	Quality-weighted for brand use: SP		
	Formal sector	83.1% (70.0 to 90.0%)	Further analysis of Table 7.6
	Retail sector	83.4% (70.0 to 90.0%)	
Q_U	Quality-weighted for brand use: AQ		
	Formal sector	84.7% (70.0 to 90.0%)	Further analysis of Table 7.6
	Retail sector	81.4% (70.0 to 90.0%)	

* Plausible range for sensitivity analysis (worst and best case scenario as in Chapter 7)
† na-not applicable
‡ Formal sector- GoK clinics and hospitals, not-for-profit clinics and hospitals, and Community Health Workers (CHW)
§ Retail sector- General retail shops, drug vendors and pharmacies
‖ 95% confidence interval
¶ "Adequate prescription"-those prescribed an adequate dose or higher than recommended. Inadequate adherence-prescribed lower dose than recommended
** "Adequate adherence"-those who took an adequate dose or higher than recommended. "Inadequate adherence"-took lower dose than recommended.

By multiplying the estimates from steps one to three, the overall community effectiveness of SP was estimated to be 12.4% (0.9 to 42.3%); 11% (0.7 to 35.9%) in the formal sector and 1.4% (0.2 to 6.4%) in the Retail sector. That for AQ was estimated to be 2.4% (0.3 to 13.0%); 0.9% (<0.1 to 4.4%) in the formal sector and 1.5% (0.2 to 8.6%) in the retail sector (Figure 8.2).

Figure 8.2: An example of community effectiveness of first and second-line antimalarial drugs in Kenya



If ART-LUM, the proposed first-line policy, is taken up to the same extent as SP in the formal sector (where it will be introduced first), and prescription behaviour does not change (and using the drug effectiveness estimates from Chapter 7), the combined community effectiveness for ART-LUM is projected to be 18.6% (1.8 to 50.6%). This is despite the fact that the drug has been assumed to be available through the formal sector only; if it availed in the retail sector at cost, the community effectiveness will increase.

There are two main, implicit assumptions made in this final chapter: 1) that patients who adhere to medications adequately will benefit more from them than those who do not; 2) that there is a linear relationship between the parameters used in Figure 8.1. The limitations of the later assumption as far as drug effectiveness is concerned have been discussed in Chapter 7 and a recent review by Yeung & White (2005) suggests indeed that for the artemisinins, even a less than perfect adherence affords better outcome than intuition would have suggested for drugs with a complex dosage regimen. This is certainly welcome news, but more data are needed to better model community effectiveness and more specifically, the contribution of adherence to drug effectiveness.

The second assumption of linearity between access and drug effectiveness (to afford a combined estimate) might not hold for all patients as well. In classical pharmacology, it is acknowledged that therapeutic outcome is not always dependent on drug factors alone, but that a dynamic interplay between host factors, parasite factors, and product factors results in a favourable or unfavourable outcome. Most patients with mild malaria recover without recourse to drugs owing to natural immunity, and of those who do not; very few will progress to severe malaria. In short, more data and a better understanding of the interplay between the factors in community effectiveness are required to produce better models.

8.4 Conclusion

Providing effective drugs only is not the panacea to effective therapeutic drug policies, particularly if they remain inaccessible to rural populations at risk in Kenya. The RBM targets on prompt, effective treatment of fevers are unlikely to be met without an increased investment in behaviour change initiatives and provision of effective and affordable therapeutics at all levels of the health service, including the retail sector. International

funds are required to ensure the community effectiveness of ART-LUM since Kenya cannot afford it.

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Appendices

APPENDIX I

Abdinasir Amin, Kenya Medical Research Institute (KEMRI)/Wellcome Trust Collaborative Programme, Nairobi, Kenya.

PhD Research Questions. **Views and experiences of Kenyan academia on drug regulation**

I am trying to gather the views and experiences of academia, industry, and regulators on drug regulation in Kenya and the United Kingdom. I am specifically interested in the regulation of antimalarial drugs and how 1) this compares with that of other drugs e.g. anti-diabetics 2) how this differs between countries 3) and how the process has applied to newly registered antimalarial and anti-diabetic products. With your permission, I would like to tape-record our conversation, as this would enable me to concentrate on the conversation better and to also accurately analyse the data collected afterwards. The information you provide will be kept confidential and will be used only in this thesis.

Thanking you in advance.

Abdinasir Amin, PhD student. Supervised by Professors Robert Snow, Tom Walley, Gilbert Kokwaro, and Peter Winstanley.

Questions

1. Could you briefly tell me about your academic interests?
2. Could you describe for me the history of drug regulation in Kenya?
3. How about that of the pharmaceutical industry in Kenya?
4. How are drugs supplied: in the public sector? In the private sector?
5. How are drugs regulated in this country?
6. What is the role of drug regulation Kenya?
7. How is a balance maintained between the need to promote local industries on one hand (economic need) and the need to regulate industry (public health need)
8. What criteria are used to register new drugs?
9. In your experience/opinion, do the criteria differ for different drugs?
10. What happens after the drug is in the market?
11. Do you have any views on drug regulation in the developed countries e.g. UK?
12. Does the process differ from the developing world Kenya? In what ways?
13. Is there anything you would like to add on?
14. Do you have any questions for me?

Thanks once again.

APPENDIX II

Serial No [__][__][__][__]

COMMUNITY SURVEY: PROJECT 1586
(Form DOMC/HH1)

District-Enumeration-Homestead number –[__]-[__|__|__]-[__|__|__]

Section 2: Childhood fevers

Identify all resident children below 5 years of age and put their names in a hat or bag to randomly select one child. If there is no child aged less than 5 years go to section 3.

No. of substitutions made..... ..... [__] **No. of these which were refusals ..... [__]**

QUESTIONS & INSTRUCTIONS	RESPONSES	GO TO
32. Child's name/ ***Jina la mtoto.***	[_____]	
33. Mother's name/ ***Jina la mama mtoto***	[_____]	
34. Father's name // ***Jina la baba mtoto***	[_____]	
35. Child's sex (M/F)/ / ***mtoto wa kike au kiume***	[__]	
36. Child's date of birth (dd-mm-yy)/ ***Tarehe ya kuzaliwa (siku/ mwezi/ mwaka***	[__|__]-[__|__]-[__|__]	
37. Does the child sleep with the mother (Y/N) / ***Na huyu mtoto hulala pamoja na mama***	[__]	
38. Does the child sleep on 1. A bed with a mattress; 2. A bed A bed without a mattress; 3. On a mattress or mat on the floor/***Je huyu hulalia 1. Kitanda kilicho na godoro 2. Kitanda kisicho na godoro 3.kwa godoro au mkeka chini?***	[__]	
39. Does the child <u>usually</u> sleep under a bed net (Y/N) / ***Je huyu mtoto hulala kwenye/ndani ya neti kwa kawaida.***	[__]	IF NO GO TO 48
41. If .yes, did the child sleep under a bed net last night (Y/N/D)/ ***Kama ndio, huyu mtoto alilala kwenye/ndani ya neti usiku uliyopita (N / L)***	[__]	
42. From whom was the bed net purchased/obtained ***Neti hiyo ilinunuliwa au kupatikana Kutoka kwa nani.***	[_____][__]	
43. How much did the net cost – if free indicate 0000 (KES) / *Hiyo neti iligharimu pesa ngapi*	[__|__|__|__]	
44. Has the net ever been treated with dawa (Y/N/D)? / ***Hii neti imeshawahi kutiwa dawa***	[__]	IF N/D GO TO 48
45. If yes, was the net treated in the last 6 months (Y/N/D)/ ***Kama ndio, je ilitiwa dawa katika miezi sita iliyopita***	[__]	IF N/D GO TO 48
46. If yes, where and who treated the net/ Kama ***ndiyo, ilitiliwa dawa mahali gani na ni nani alit\yeitia dawa***	[_____][__|__]	
47. How much was paid for the net treatment – if free indicate 000 (KES)/ ***Ni pesa ngapi zilitumika kutia neti hii dawa***	[__|__|__]	
48. Does the child sleep in a room where the walls have been sprayed with a long lasting insecticide within the last 12 months (Y/N)/ ***Je mtoto hulala kwa chumba ambacho kutaZake zimenyunyiziwa dawa ya mbu inayodumu muda mrefu katika miezi kumi na miwili Iliyopita?***	[__]	IF NO GO TO SECT. 3
49. Has the child had a fever or hot body in the last 14 days (Y/N)/ ***Na mtoto amewahi kuwa nahoma au mwili wenye joto sana katika siku kumi***	[__]	

na nne zilizopita		
50. For how many days was/has the child been unwell/ *Ni kwa siku ngapi huyu mtoto amekuwa hajisikii vizuri.*	[__|__]	
51. Is the child suffering from a fever or hot body TODAY (Y/N) */Huyu mtoto ana homa au joto Jingi mwilini leo*	[__]	

Serial No [__][__][__][__]

District-Enumeration-Homestead number –[__]-[__|__|__]-[__|__|__]

53. If yes, complete the following treatment history as per your training and manual/

52. Has the child received any treatment for this fever (Y/N)*/ Mtoto ameshapata matibabu yoyote kwa ajili ya hali hii?*[__] ***IF NO GO TO SECTION 3***

Order	Day of illness	Where treatment sought (Codes-name of treatment source-Codes)		Anti-malarials or anti-pyretics Codes& # tabs/spoons)			Money Spent (KES) (on drugs)	(transport)	(consult.)
		PLACE	NAME						
1.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
2.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
3.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
4.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
5.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
6.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
7.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
8.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]
9.	[__|__]	[__|__]-[_____][__|__|__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__]-[__|__]	[__|__|__|__]	[__|__|__|__]	[__|__|__|__]

54. What has been the total amount spent on drugs to treat this febrile episode (KES)..... .....[__|__|__|__]
Kwa jumla ni pesa ngapi zimetumika kwa dawa pekee wakati wa matibabu ya hii homa

55. What has been the total amount spent on transport during the treatment of this febrile episode (KES)..... .....[__|__|__|__]
Kwa ujumla ni pesa ngapi zimetumika kwa safari pekee wakati wa matibabu ya hii homa

56. What has been the total amount spent on consultation fees to treat this febrile episode / (KES)..... .....[__|__|__|__]
Kwa ujumla ni pesa ngapi zimetumika kwa ushuri wa daktari kabla ya matibabu ya homa hii.

APPENDIX III

Division of Malaria Control, Ministry of Health
Retail outlet audit
(Form DOMC/RS1)

Enumerator's Name & Code.....[_____][__|__|__]

1. Outlet **name** .....[_____]

2. Outlet **ID** .....[__]-[__|__|__|__]

3. Today's **date** .....[__|__]-[__|__]-[__|__]

4. **Position**:

District.....[_____][__]
Location.....[_____][__|__|__]
Sub-location .....[_____][__|__|__]
Enumeration Area name.....[_____][__|__|__]
Longitude .....[__]-[__|__]-[__|__|__|__|__]
Latitude .....[__]-[__|__|__]-[__|__|__|__|__]

5. Type:

Category A: 1. Rural or 2. Urban (*see notes*).....[__]

Category B: 1. Private pharmacy; 2. Large Duka (*see notes*);
3: Small Duka/Kiosk (*see notes*) .....[__]

6. **Advertising**

a. Does the outlet have branded wall painting advertisement for malaria products (Y/N) .....[__]

-If yes, indicate branded product (s)

Brand 1 .....[_____]-[__|__|__]
Brand 2 .....[_____]-[__|__|__]
Brand 3 .....[_____]-[__|__|__]
Brand 4 .....[_____]-[__|__|__]
Brand 5 .....[_____]-[__|__|__]

b. Does the outlet have branded advertising materials on display that are not wall paintings for malaria products (AM & AP brands, nets, insecticides, etc) (Y/N) .....[__]

-If yes, indicate all branded products advertised:

AM brands

Brand 1 ..... [_____]-[__|__|__]
Brand 2 ..... [_____]-[__|__|__]
Brand 3 ..... [_____]-[__|__|__]
Brand 4 ..... [_____]-[__|__|__]
Brand 5 ..... [_____]-[__|__|__]
Brand 6 ..... [_____]-[__|__|__]
Brand 7 ..... [_____]-[__|__|__]

AP brands

Brand 1 ..... [_____]-[__|__|__]
Brand 2 ..... [_____]-[__|__|__]
Brand 3 ..... [_____]-[__|__|__]
Brand 4 ..... [_____]-[__|__|__]
Brand 5 ..... [_____]-[__|__|__]
Brand 6 ..... [_____]-[__|__|__]
Brand 7 ..... [_____]-[__|__|__]
Brand 8 ..... [_____]-[__|__|__]
Brand 9 ..... [_____]-[__|__|__]
Brand 10 ..... [_____]-[__|__|__]

Comment Box on advertising

Interview person found in shop

7. Date business was established **(mm/yy)**..... [__|__]-[__|__]

8. Name of main seller ..... [_____]

9. **Details** of main seller:

Age (years)..... [__|__]
Sex (M/F) ..... [__]
Level of education attained (***specify***)..... [_____]
How long has **main seller** worked in outlet (years) ..... [__|__]

10. Details of other respondent **if not main seller**

Name ..... [_____]
Age (years)..... [__|__]
Sex (M/F) ..... [__]
Level of education attained (***specify***)..... [_____]
How long has **respondent** worked in outlet (years)..... [__|__]

Comment Box on respondent(s)

11. **Types of drugs** available for sale **today**: (AM = anti-malarials; AP = Anti-pyretics)

Mark (Y/N)

Antimalarial (AM) ..... [__]
Anti-Pyretic (AP) ..... [__]
Anti-Diarrhoeal ..... [__]
Cough/Cold medication ..... [__]
Worm medication ..... [__]
Other (*specify **only for shops;** not pharmacies)* ..... [__]

Specify other 1 ..... [_____]

Specify other 2 ..... [_____]

Specify other 3 ..... [_____]

Specify other 4 ..... [_____]

Specify other 5 ..... [_____]

Comment Box type of drugs available today

Outlet ID [__]-[__|__|__|__

12. Types of **AM** and **AP** drugs currently in shop (*examine packages and refer to notes 1 to 6 below*): **Use notes to fill both 12a and 12 b**

Notes:

1. **Brand Name:** Put down what's on package. **Record adult and junior preparations separately**
2. **Brand Code:** See drugs coding sheet for codes
3. **Chemical Type:** Code (1) for Amodiaquine products, (2) SP, (3) Chloroquine, (4) Quinine, (5) Halofantrine, (6) Mefloquine, (7) Dihydroartemisinin, (8) Artesunate, (9) Artemether, (10) Artether, (11) Proguanil (12) Pyrimethamine (13) Artemether+Lumefantrine (14) Paracetamol, (15) Aspirin and (16) products with both Aspirin and Paracetamol (17) Ibuprofen (18) Para cetamol & Ibuprofen (19) Others
4. **Retail price per unit:** For instance most SP and Amodiaquine tablets come in units of 3. If suspension, quote price per bottle and specify bottle e.g. Ksh. 30 per 60ml bottle
5. **Expiry:** Use format 00/00 (Month/Year). For loosely packed drugs with no expiry on package, use NA (Not Applicable)
6. **Storage:** Code (1) Off floor, (2) Out of direct sunlight, (3) Dry area, (4) Away from foodstuff, (5) All conditions met. **NB can have more than one answer.**

a) AM Drugs

Brand name	Brand code	Chemical type	Wholesale source	Retail price (per unit)	Expiry date	Storage

b) AP Drugs

Brand name	Brand code	Chemical type	Wholesale source	Retail price (per unit)	Expiry date	Storage

Most common AP brand **among the above** .....[_____]-[__|__|__]

13. **Other shop resources**: Indicate if the following are present **today**:

a. Division of malaria control leaflets (*see notes*) (Y/N) ..... [__]

b. Division of malaria control posters (*see notes*) (Y/N) ..... [__]

c. Bed nets (Y/N)..... [__]

-If yes, **brand names, retail prices** and **quantity currently in stock**
(*If not branded, indicate* ***source***)

Brand 1/Source 1[_____]-[__|__|__|__]-[__|__|__]-[__|__]
Brand 2/Source 2[_____]-[__|__|__|__]-[__|__|__]-[__|__]
Brand 3/Source 3[_____]-[__|__|__|__]-[__|__|__]-[__|__]

d. Insecticides for treating bed nets (Y/N) ..... [__]

-If yes, **brand names** and **retail prices** (*if not branded, indicate* ***source***)

Brand 1/Source 1.....[_____]-[__|__|__|__]-[__|__]
Brand 2/Source 2.....[_____]-[__|__|__|__]-[__|__]
Brand 3/Source 3.....[_____]-[__|__|__|__]-[__|__]

e. Insecticides for indoor residual house-spraying (Y/N) ..... [__]

-If yes, **brand names** and **retail prices** (*if not branded, indicate* ***source***)

Brand 1/Source 1.....[_____]-[__|__|__|__]-[__|__]
Brand 2/Source 2.....[_____]-[__|__|__|__]-[__|__]

f. Mosquito coils (Y/N)..... [__]

g. Aerosol insecticides (Y/N)..... [__]

h. Mosquito repellent body gels/creams (Y/N)..... [__]

Comment Box on malaria resource materials

14. ***Now ask respondent the following questions:*** *(if not main seller, respondent needs at least 3 months in shop or pharmacy for data to be valid)*

a) Do you **ever** give advice on how drugs in your shop **should be used**? (Y/N).....[__]

b) If yes, **what advice** would you give about _____ tab/susp (*one of the AM brands stocked*) for an **adult**? *Record response* ***verbatim*** *below.* ***Probe for every advice given***

c) **For this same brand**, if a mother asked you **how much** she should give to her **child of 2 years,** how would you advice her? *Record response* ***verbatim*** *below.* ***Probe again for every advice given***

d) Did the shopkeeper consult a **drug reference material** in **c)** above? (Y/N).....[__]

-If yes, describe the reference .....[_____]

15. As per retailer's experience, which are the **most popular AM brands** (*in order of preference)*

Brand I..... [_____]-[__|__|__]
Brand II ..... [_____]-[__|__|__]
Brand III..... [_____]-[__|__|__]
Brand IV..... [_____]-[__|__|__]
Brand V ..... [_____]-[__|__|__]

16. Why does retailer think his/her customers prefer them to other similar products? ***Probe for all possible reasons***

17. Ask the retailer to **quantify** the **retail turnover** of these brands I to V in terms of number of tablets or bottles of syrups/suspensions sold **per week**:

Brand I. [_____]-[__|__]-[__|__|__]
Brand II [_____]-[__|__]-[__|__|__]
Brand III[_____]-[__|__]-[__|__|__]
Brand IV[_____]-[__|__]-[__|__|__]
Brand V[_____]-[__|__]-[__|__|__]

18. Has the shop/pharmacy being visited in the last 12 months by MoH inspectors? (Y/N) .....[__]

Comment Box on Q15-Q19

General Comments on this Retail Outlet:

1.

2.

3.

4.

5.

APPENDIX IV

Division of Malaria Control, Ministry of Health

Anti-malarial Drug Wholesalers Survey (Form DOMC/RS4)

Enumerator's Name & Code.....[_____][_|_|_]

1. Wholesaler's ID .....[_]-[_|_|_|_]

2. Wholesaler's name.....[_____]

3. Owner's name .....[_____]

4. Location

District [_____][_]
Location.....[_____][_|_|_]
Sub-location .....[_____][_|_|_]
Enumeration Area name [_____][_|_|_|_]

Longitude [_]-[_|_]-[_|_|_|_|_]

Latitude..... [_]-[_|_|_]-[_|_|_|_|_]
Physical address .....[_____]
Telephone number.....[_____]

5. Today's date.....[_|_]-[_|_]-[_|_]

6. Following explanation of the purpose of the survey did the wholesaler agree to participate in the survey (Y/N) .....[_]

If yes, continue

Brand Sampled	Chemical Code (AQ/SP)	Brand Code	Number of tablets/etc purchased	Cost per unit	Storage conditions (see notes)